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SYPHILIS

SYPHILIS

A TREATISE ON ETIOLOGY, PATHOLOGY, DIAGNOSIS, PROGNOSIS, PROPHYLAXIS, AND TREATMENT

BY

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TO

DR. EDWARD A. BALLOCH,

A GOOD FRIEND,

THIS BOOK IS DEDICATED

PREFACE

At the present time there exists no small book that covers the whole field of syphilis in an authoritative way. To know syphilis means to know the entire domain of medicine, and for any one man this is impossible. In the preparation of this work I have been fortunate in being able to induce various men to write special chapters for me. Major Matthew A. Reasoner has contributed the sections on Infection and Immunity; Dr. H. A. Fowler has treated the subject of Syphilis of the Male Genito-urinary Organs; while Dr. John Dunlop has written the major portion of the chapter upon the Bones, Joints, Muscles, Tendons and Bursæ. Dr. John Lind, Senior Physician at St. Elizabeth's Hospital, has taken the whole subject of the Central Nervous System, a chapter to which Dr. Wm. H. Hough has contributed freely from his large practical and laboratory experience. Drs. Virginius Dabney and L. H. Greene have written respectively on the Ear and Eye. Colonel Chas. F. Craig has covered the Wassermann Reaction in both Diagnosis and Treatment. Dr. Jay F. Schamberg has written on the Toxicology and Therapeutic Testing of Arsphenamine, Capt. Walter Van Sweringen, formerly radiographer at the Freedmen's Hospital, where most of my work has been done, has furnished the radiograms and written on the subject of Diagnosis from the Radiographer's Standpoint. Dr. Edward Hiram Reede has assisted me greatly in the chapter concerning the Endocrine Glands. Drs. John A. Fordyce and Geo. M. MacKee have given me many excellent photographs, and Dr. Richard L. Sutton has kindly permitted me to use such of his material as I saw fit. Many other friends and acquaintances have aided in various ways, either with illustrations or advice, and to them I give my thanks, for much of the best in this book is due to others.

H. H. Hazen.

Washington, D. C.

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SYPHILIS

CHAPTER I

INTRODUCTION—HISTORY—OCCURRENCE—ECONOMIC IMPORTANCE

Introduction

Syphilis, which is often spoken of by medical men as lues or specific infection, and by the laity as pox, dry pox, or the bad blood disease, is the result of a chronic infection with the Treponema pallidum, and is characterized by more or less severe lesions in any portion of the body. Because of its frequency, of the many diseases which it may imitate, of its complications, and of its serious late consequences, it is one of the most important medical diseases which we have to combat. Every field of medicine is directly invaded: no organ of the body is exempt.

Within the past ten years our conceptions of syphilis have been materially changed by a number of discoveries. The causal organism has at last been found and the disease reproduced with it. The introduction of the Wassermann reaction and of its various modifications has given us the greatest assistance in diagnosis; and lastly the use of arsphenamine and of the later arsenic compounds has provided far and away the best means of combating the disease.

History

As has been pointed out by many authors, most recently by Howard Fox,[1] there has been much discussion as to whether or not syphilis was referred to in the Bible and in various of the ancient medical writings, and at present it is generally conceded that no description that fits the affection can be found therein. There are several recent descriptions of the early history of the disease that merit attention. The most pretentious of these is the exhaustive article by Bloch,[2] but the articles by Pusey[3] and

Osler[4] are also excellent, and the following account is derived from all of them.

All authors agree that it was not until 1494, during the raid of Charles VIII upon Italy that the disease really attracted attention. The movements of an army of over thirty thousand men with the usual crowd of camp followers and prostitutes, the lack of any severe early fighting and the effeminate luxury of Italy at that period made the campaign one of debauchery rather than of warfare. In 1495 the army was forced to retreat, and the troops, who were mainly mercenaries, wandered back to their homes as best they could. The local development of syphilis in Italy can be traced to the influx of Charles' army, and the spread of the malady over the rest of Europe to the time when his soldiers fled from the country and scattered themselves over the continent. So syphilis first appeared in France, Germany, and Switzerland in 1495, in Holland and Greece in 1496, in the British Isles in the following year, and in Russia in 1499. From Europe the disease was carried to the Orient by the great voyagers, not reaching Japan until 1569. It is usually stated that the disease was much more virulent than at present, in other words that it attacked with the vigor of a new disorder, a statement to which Fordyce[5] takes exception. In 1530 Fracastorius wrote his celebrated poem which deals with the punishment by the gods of a certain shepherd named Syphilus for his blasphemy. The name "syphilis" dates from the time when this poem was published. The etymology of the word syphilis is uncertain, but probably comes from σιφλός, crippled or maimed.

The origin of syphilis has been the subject of much speculation. The mere fact that it first appeared in Europe after the return of Columbus lent plausibility to the theory that the disease had an American origin and that it was taken to the old world by the discoverers, especially as there were many Spaniards in Charles' army. Later research has tended to confirm this view, for no syphilitic bones of early date have been discovered in Europe. In 1882 Montejoy Robledo[6] critically examined many early manuscripts. His most important discovery was the finding of a document written by Ruy Diaz de Isla, a physician of Lisbon, who attended many of the sailors of Columbus for syphilis when they returned to the continent. Seler[7]

deserves credit for calling attention to Robledo's work. This account has been corroborated by the writings of Oviedo and Las Casas. It seems probable that the disease had its origin in Haiti, although it may have existed also throughout Central America, for there have been various reports of syphilitic bones of an early date throughout this region. There is really nothing mysterious in the confusion that surrounds the early history of syphilis, for this darkness is also true of practically every other disease.

Occurrence

Syphilis is a common disease. As shown by the figures of the American Dermatological Association, given by Pollitzer,[8] it constitutes practically 10 per cent of all dermatoses. Now that routine Wassermanns are being done in many of our hospitals, it is found that from 20 to 30 per cent of all admissions give a positive reaction. For instance, Greeley[9] states that at Bellevue Hospital in New York City 22 to 25 per cent of all patients give a positive reaction. He also shows that of 1117 tests upon supposedly healthy applicants for license to peddle, 8.4 per cent gave a similar finding. Vedder and Hough[10] have shown that in an insane asylum the reaction is positive in about 20 per cent of the men, in a few white women, but in 12 per cent of the negro females. Walker and Haller[11] report from Boston 600 cases giving a positive complement-fixation test in 4000 admissions to a general hospital. Moore,[12] of Chicago, reports 418 routine examinations of dispensary cases with 56 positive findings. Churchill[13] found that 28 per cent of 101 children examined at a children's hospital had syphilis, while Lucas[14] reported a trifle higher percentage. Browning[15] found 14 per cent of syphilitics among 331 dispensary children of Glasgow and that among prostitutes and tramps practically all had been affected. Based solely upon clinical ground, Neisser estimated that 12 per cent of the adult population of Berlin was syphilitic, while Fournier considered that 15 per cent of the adult Parisians had suffered from the disease.

When it is remembered that the Wassermann reaction is frequently negative during the latent stages of syphilis, it seems not improbable that 10 per cent of the adult male population of the United States is definitely syphilitic. It is interesting to

note that practically all observers are agreed that the percentage of syphilis among women is much lower than among men.

Occurrence in Negroes

As both Boas[16] and I[17] have pointed out, it is extremely difficult to obtain accurate figures as to the prevalence of syphilis in the negro race, although it is usually conceded that this disease is more prevalent among them than among whites. Howard Fox,[18] Boas and myself believe that among the hospital class syphilis is about one and one-half times as frequent as among the hospital class of whites. Fox's figures are particularly instructive. He found the following:

		Number of cases	*Syphilitics per cent*
Patients with general diseases	Whites	15,000	3.96
	Blacks	32,000	5.82
Patients with skin diseases	Whites	2,200	12.00
	Blacks	2,200	27.00

The report of the Surgeon General[19] of the United States Army is also interesting:

	Race	*Number of men*	*Ratio per 1000 luetic*
Enlisted men of the whole army	White	76,135	22.66
	Black	4,631	32.39

Ivey's[20] reports of cases among the insane show the following results:

	Number of cases	*Per cent of positive Wassermanns*
White males	420	6
Negro males	255	16
White females	351	5
Negro females	218	16

It is only surprising that the percentage of syphilitics among this unfortunate race is not much higher. During the days of slavery the negro was usually well looked after by his master, for he was valuable property, just as a horse or cow was. On the other hand too little attention was paid to his moral development, and husbands and wives were frequently separated by the

auction block. After slavery was abolished the negro was free to live as he liked, but had never been educated as to how to protect either himself or his race. The southern whites naturally frowned upon his material advancement as that only too justly seemed to them a prelude to political power, and the political power of the negro, especially when aided by the carpetbagger, was a thing to be dreaded. Then too he was forced to share in the general postbellum poverty of the south. As a result he was forced to live under the most wretched circumstances. Whiskey and cocaine speedily levied their tolls upon him and have been the cause of much suffering and much crime. Taken all in all the race has done remarkably well.

Economic Importance

Unfortunately there are very few articles that deal with this aspect of syphilis, although it is generally admitted that syphilis causes serious economic losses. According to the census reports, syphilis does not cause over three thousand deaths a year in the United States, but when one studies the deaths due to various disorders usually or invariably produced by syphilis, he must be led to the conclusion that Leredde[21] is right when he says that lues annually causes twenty-five thousand deaths in France. The census reports of the United States for the year 1909 give the following figures as to the causes of death:

Syphilis	2,858
Encephalitis	355
Tabes	1,386
Apoplexy	36,463
Softening brain	1,126
Paralysis	7,669
Paresis	2,584
Angina pectoris	3,481
Heart disease	65,971
Bright's disease	43,412
Arteries	10,174
Cancer mouth	1,427

Now we are probably justified in assuming that all cases of death from apoplexy, angina pectoris, and paralysis occurring in subjects less than forty years of age are due to syphilis. In

view of the known frequency with which the virus of lues attacks the arteries, it is probable that at least 10 per cent of the deaths due to diseases of the heart and kidneys can also be attributed to this infection. We are also probably on thoroughly safe ground when we estimate that one-half of the deaths due to diseases of the arteries (including aneurysm), to encephalitis, to "softening of the brain," and to cancer of the mouth are directly due to syphilitic infections. Granting these assumptions, we have the following figures:

Syphilis	2,858
Encephalitis	177
Tabes	1,386
Apoplexy	1,580
Softening brain	563
Paralysis	327
Paresis	2,584
Angina	225
Heart disease	6,597
Bright's disease	4,341
Arteries	5,087
Cancer mouth	713
	26,438

When we further consider that some of the cases due to cirrhosis of the liver, possibly some cases of pernicious anemia and various other not infrequent affections are syphilitic in origin, it is probable that the above figures do not represent the total number of deaths due to syphilis. These figures are fairly well borne out by the life insurance reports which show that the expectancy of life in syphilitic subjects is decreased from one-third to one-fourth. Brockbank[22] gives the following reports from the American insurance companies as to the fate of the syphilitic insured:

Age periods	*Number policies issued*	*Number of deaths*	*Expected deaths*
15-28	1,117	45	42.8
29-42	3,291	232	172.5
43-56	909	107	69.8
57-70	68	13	12.8

While these deaths were not necessarily due to syphilis, yet despite all care in selection, the mortality among those who had a history of syphilis was 33⅓ per cent above expectations.

In addition to the number of deaths that directly result from this infection, syphilitic women do not bear the number of living children that they otherwise would. Many of the miscarriages are directly attributable to syphilis, so are many of the early deaths among the newborn. In addition to the loss of life, it must be remembered that much time is lost from useful occupations and much money spent in doctors' and druggists' bills. In other words, there is a marked loss in the productive capacity of practically every individual afflicted with this disorder. It is probably fair to assume that two hundred thousand individuals each suffer a pecuniary loss of one hundred dollars a year because of being syphilitic, or at least twenty million dollars a year for the population of the United States. If the number of the hopelessly incapacitated be added and the productive value of each be estimated at five hundred dollars annually, this amount will be greatly increased. If in addition, the interest on money that is invested in hospitals and clinics where these patients are treated either for syphilis or for diseases due to syphilis be added, there will be another substantial increase. In fact it is probable that the total economic loss is nearly half a billion dollars a year to the United States alone. In addition to this financial loss there is an immense amount of suffering, both among the innocent and guilty, many separations in families, and losses in a thousand and one ways.

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CHAPTER II

ETIOLOGY

As Osler[1] well remarks "the story of the search for the cause of syphilis is a tale to make the judicious grieve." In 1905 Lassar stated: "One hundred twenty-five causes of syphilis have been established during the last twenty-five years." The earlier history as to its relationship to gonorrhea and chancroid is not particularly elevating. John Hunter,[2] the great English physiologist and surgeon, as the result of an experiment, whereby he inoculated himself with supposedly gonorrhea pus and later developed syphilis, taught that there were three kinds of venereal infection, gonorrhea, chancre, and lues venerea, and that all were the result of the same poison, the only difference being the nature of the surface upon which the virus acted. Bell,[3] both as the result of experimental work and of clinical observation, could not accept these doctrines and consistently fought against them. Ricord in 1838 made the first impression as to the differences between syphilis and gonorrhea. Ricord's pupils, Bassereau, Clerc and Fournier clearly showed that syphilis and chancroid were two distinct affections.

From time to time many different organisms were described as the true causes of syphilis. The history of these false hopes is well described by Pasteur.[4] The two most important were the bacillus of Lustgarten,[5] described in 1885, and the Cytoryctes luis of Siegel.[6] The latter is of importance because it started Schaudinn on his work that eventually led to the discovery of the true cause.

The protozoologist, Fritz Schaudinn, and the syphilologist, Erich Hoffmann, first demonstrated the presence of spirilla in a chancre on March 3, 1905. The publication of the first reports[7] led to an immense amount of work, and the discovery was speedily verified from many sources. The organism was at first called the Spirocheta pallida but is now known as the Treponema pallidum.

Nichols[8] compares the appearance of the organism to that of a spirally wound wire. It is from four to fourteen microns in length and has a thickness of about one-quarter of a micron, and contains from six to fourteen spirals, which are close set and regular. Occasionally larger specimens with more windings are found. No internal structure can be demonstrated. The parasite is extremely motile, and there is a considerable amount of lateral flexibility.

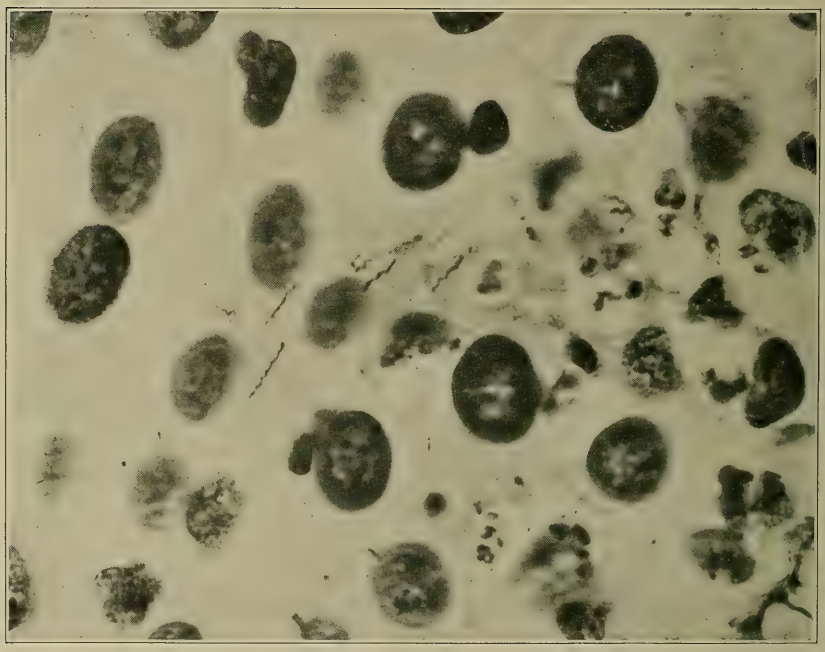

Fig. 1.—This section from the wall of a hair follicle in secondary syphilis shows well the structure of the Treponema pallidum. (Courtesy of Dr. C. C. Dennie.)

As yet we know practically nothing concerning the life history of the organism. McDonagh[9] believes that the form that we know is simply the male gamete of a sporozoan parasite, and that the other forms can be demonstrated in the lymph glands by means of a pyronin and methyl green stain, and *in vivo* with borax methylene blue. However, his work has not found general acceptance, largely because of the fact that the treponema can be cultivated for hundreds of generations and only one form found.

The treponema is present in large numbers in the primary and secondary lesions, and has even been demonstrated in the brains of paretics. During the acute stage it can be found in the blood and in various of the secretions of the body, although not in large numbers.

The organism was grown in pure culture by Noguchi[10] in 1911. He obtained his first growth by inoculating one part of ascitic fluid and three parts of distilled water to which a bit of fresh rabbit testicle was added, and incubating under anaerobic conditions. After a growth was started it was continued in filtered ascitic fluid one part, agar two parts, with a piece of sterile normal tissue added and covered with paraffin oil. From human lesions inoculations can be made direct upon the latter media. Noguchi has been able to reproduce the disease with material from his cultures.

Haensell[11] in 1881 first successfully reproduced syphilis in the anterior chamber of the eye in laboratory animals, but his work attracted little attention because the specific nature of the reaction could not be demonstrated. In 1903 Metchnikoff and Roux[12] first transmitted the disease to apes, and it has since been found that rabbits are excellent animals upon which to work. A good resume of these early attempts at inoculation has been published by Williams.[13] Uhlenhuth and Mulzer,[14] in 1910, developed this field much more fully.

According to Noguchi's[15] recent very complete article the spirochetes may be divided into four genera: the spirocheta, cristispira, saprospira and spironema and treponema.

Spirocheta.—Unlike the other spiral organisms, members of this genus do not swim, but their movement is effected by a creeping movement along the surface of some object. Multiplication is brought about by transverse fission. They are not responsible for any diseased conditions so far as is known at present.

Cristispira.—This genus was created by Gross in 1910 for large saprophytic spiral organisms found in the alimentary tract of certain shell fish. They are characterized by a ridge or crista which extends spirally along the whole length of the body. The cell body is surrounded by a strong membrane similar to that found in bacteria. Division is exclusively transverse.

Sporulation has been described. There are eighteen known species which inhabit different varieties of shell fish.

Saprospira.—The saprospira are mussel spirochetes that have no ridge, although they otherwise resemble the preceding genus.

Spironema and Treponema.—Noguchi, after a brief review of the subject, states that the difference between these two groups is one of degree, not of quality. They all have slender, cylindrical, spirally wound, highly flexible bodies, which exhibit serpentine, corkscrew-like, and sometimes lashing movements. The more active an organism is the less rigid are its curves. The treponema group exhibits a less energetic motility than does the spironema group. The body of spironema is much heavier than that of the treponema. On the surface of the cell body there is a thin membrane which can be detected when the organism undergoes degeneration. There is a terminal appendage projecting from the end of the cell body and which resembles a thread. No motility can be determined in this appendage, which may be bent at right angles to that of the cell body. It is generally believed that these organisms undergo transverse division like bacteria. Noguchi thinks that longitudinal fission is also possible in some of them. There is some question concerning spore formation. Members of this genus are parasitic and many diseases are due to them. This genus may again be classified as follows:

1. Varieties which invade the blood principally.

A. Those which cause characteristic fevers known as relapsing or tick fevers.

B. Those which do not seem to cause any grave condition, but are incidentally found (not in man).

2. Those which invade the tissue primarily.

A. Those which cause characteristic lesions and symptoms: the two members of this group occurring in man are the Treponema pallidum and the Treponema pertenue of yaws.

B. Those which do not seem to cause any noticeable lesions.

3. Varieties which invade both the blood and tissues indifferently. In this group belongs the organism causing Weil's disease.

4. Varieties which may be associated with certain pathologic conditions and some of which are regarded as having a more in-

timate relation to the lesion than that of mere secondary invaders. Included in this group are the organisms of Vincent's angina and of various tropical ulcers.

5. Varieties which are found in or about body cavities, alimentary canal and genitals.

Viability

The organism of syphilis quickly becomes sluggish after being removed from the living tissue, and motility can seldom be detected in any specimen which has been maintained at body temperature for twenty-four hours. On the other hand, treponemata contained in tissue may be infective if kept at room temperature for forty-eight or even seventy-two hours. Postmortem material containing organisms is infectious at the end of twenty-four hours. The viability of cultural strains is much greater than that of organisms in the tissues. In undisturbed cultures T. pallidum may remain alive for one year at body temperature and five months at a temperature of 15° C. In a refrigerator at 2° C. it may survive for two months. The organisms will resist the direct rays of the sun for nearly five hours. Drying promptly kills them. The thermal death points are as follows, 55° C. 10 minutes, 60° C. less than five mintues. Turning to the antiseptics we find that the treponemata are killed as follows:

Lugol's solution	1:3 dilution	1:10 in 15 minutes
Bichloride	1:5,000	1:10,000 in 15 minutes
Phenol	1:200	1:1,000 in 30 minutes
Lysol	1:1,000	
Formalin	1:200	
Potassium permanganate	1:1,000	1:5,000 in 15 minutes
Salvarsan	1:7500	
Neosalvarsan	1:2,500	
Potassium iodide	1:10	

Akatsu has found that he can cause the resistance of treponemata to be raised to the mercurials and also to some extent to arsphenamine by growing the organisms in a culture containing traces of these substances. This is much more marked in the case of mercury than in the case of arsphenamine.

Filterability

Treponema pallidum is unable to pass through any bacteria-proof filters when the usual processes are employed. On the other hand it can grow through the pores of a Berkefeld filter.

Relationship to Yaws

There has been much discussion as to the relationship of yaws and syphilis. Russell,[16] Castellani,[17] and others have shown that the two organisms differ morphologically, and usually the diseases run different courses in animals that have been inoculated, especially it should be noted that the histopathologic pictures are essentially different. However, Reasoner tells me that in certain recent experiments he has been unable to say whether the disease that he produced was syphilis or yaws. This, coming from a man of Reasoner's experience, would seem to indicate that further work on the whole question is necessary. Hutchinson[18] has always contended that yaws was only a special modification of syphilis.

Infection

Syphilis may be either congenital or acquired. The disease is in all probability not hereditary, but the infection in the child takes place by treponemata passing through the placenta of the mother. The newer conceptions of Colles' and Profeta's laws will be discussed in the chapters on Pathology and Congenital Syphilis.

The majority of cases are acquired. Of these acquired cases about 94 per cent have the initial lesion upon the genitals, the infection being the result of sexual intercourse. In the remaining 6 per cent the primary lesion is situated upon some other portion of the skin or mucous membrane: these lesions constitute the extragenital chancres. However, such chancres are by no means always innocently acquired, for they may arise as the direct result of perverted sexual habits. The commonest of the extragenital lesions is one of the lip, and this usually results from kissing someone with a mucous patch. Schamberg's[19] report of an epidemic of such chancres is noteworthy as showing the extreme contagiousness of these chancres. In Schamberg's

cases the primary source of infection was a young man with a labial chancre. "Six young women kissed by him developed chancres of the lip. A young man present at the affair likewise developed a chancre of the lip apparently from the virus deposited on the lips of one of the young women, for he did not come in contact with the original source. In addition a young woman kissed by the offender at a third social function likewise developed an initial sclerosis, making in all eight labial chancres from the one source." Later Schamberg was consulted by another girl who had acquired a chancre of the cheek from one of the infected young women previously mentioned.

Bulkley[20] has written a very entertaining little book upon the subject of innocently acquired chancres. In addition there are many cases recorded in the literature. One of the commonest sources of extragenital infection is kissing, as has already been indicated. Next in frequency undoubtedly ranks professional infection, where a physician becomes contaminated as the result of handling a syphilitic sore. The following classification is modified from that in an article by Bulkley.[21]

I. Immediate Contact.

1. Sexual contact may give rise to chancres upon the thighs or abdomen.

2. Perverted sexual habits may cause chancres of the mouth, anus, or breast.

3. Kissing may cause chancres of the mouth or face.

4. Biting occasionally gives rise to chancres. Policemen have been infected by being bitten while making an arrest. I know of one instance where a young man struck a prostitute in the mouth, cut his hand by so doing, and developed a chancre at the seat of the injury.

5. Suckling children with congenital syphilis give rise to many initial scleroses in wet nurses. The practice of drawing the nipples has also caused many chancres of the breasts.

6. Some babes have been infected at birth as the result of coming in contact with fresh lesions upon the genitals of their mothers.

7. Instances of infection from sleeping with an infected individual are well authenticated.

8. Physicians, nurses, medical students, and midwives have only too frequently been inoculated while in the discharge of their professional duties.

9. Children have been infected by being cared for by syphilitic nurses.

II. Mediate Contact.

1. Syphilis is occasionally acquired from infected eating and drinking vessels. This can not be a common means, for cases are but rarely reported. In Russia the use of a common spoon by the peasants is the cause of many cases.

2. The use of infected water closet seats must be a very rare cause, although it is one frequently alleged by patients.

3. The use of infected towels, napkins, handkerchiefs, etc., may cause some infections. I have had one case that undoubtedly came from handling the towels of an active syphilitic.

4. Children may be infected by nursing bottles, diapers, etc. It is rather surprising that more cases are not recorded in the hospital wards.

5. The passing of vaginal syringes from one woman to another has caused a number of chancres. Likewise many cases have been reported from glass works, where one workman would infect a blowpipe and another would use it. The use of infected pipes, and even of cigars and cigarettes has caused some cases.

6. Formerly there were many cases as the result of vaccination,[22] but now that calf lymph is used there are practically no cases reported, except where the physician is responsible or where the wound is later infected. The practice of tattooing has caused more chancres than would be supposed. Ritual circumcision[23] has likewise been responsible for many an infection. When it was the practice to bleed most patients, and sterilization was unknown, many initial scleroses were induced in that way.

7. As the result of minor operations, dressings, etc., some few cases of syphilis have been caused. I have seen one chancre of the foot which developed while the patient was in a hospital for a long time.

8. The use of infected dental instruments has resulted in more than one case of mouth infection.

9. Infected eustachian catheters have caused quite a number of infections.

10. Infected razors have caused some chancres of the face.

So far there are very few cases upon record where syphilis has been transmitted from one person to another by an insect carrier,[24] but the possibility should always be borne in mind.

It is usually estimated that about 20 per cent of syphilitic infections are innocently acquired, that is, not as the result of illicit sexual intercourse. Only too frequently wives are infected by their husbands. Undoubtedly the condylomata that often linger so long about the genitals give rise to more syphilitic infections than any other type of lesion, for they simply swarm with organisms.

It is a bit uncertain how long an infected individual is dangerous to his associates. All are agreed that the disease is very contagious during the primary and secondary stages, while there is considerable doubt as to the power of an infected individual to infect any one after he has had the disease for more than four or five years. However, I am certain that I know of at least two instances where a syphilitic infected his partner over twenty years after the date of his initial lesion. The proof that treponemata are present even in as late lesions as paresis should serve to make one very cautious in asserting that the danger period soon passes.

A break in the skin or mucous membrane is usually considered to be necessary in order that the treponema may gain entrance to the body. Such minute breaks are very common during sexual intercourse.

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CHAPTER III

PATHOLOGY

The pathology of syphilis may be conveniently divided into four parts, infection, immunity, the general pathology and the special histologic pathology. Major Matthew A. Reasoner of the United States Army, who has done so much excellent experimental work on syphilis has contributed the first two sections, namely on infection and immunity.

Infection and Immunity

By Major Matthew A. Reasoner, U. S. A.

The proper study of syphilis from a scientific standpoint began with the discovery of the causal organism by Schaudinn and his confrere, Hoffmann, in March, 1905. They first gave it the name of *Spirocheta pallida,* but shortly afterward, upon a basis of morphologic characteristics, changed to *Treponema pallidum.* This latter name has been adopted by the International Committee on Nomenclature, and from the standpoint of a purist should be used. The term *Spirocheta pallida* is employed by some who are willing to accept common usage as authority. Order will never come out of the present confusion in botanical and zoological nomenclature until all of us are willing to accept a common authority; and in the very nature of things such authority can not be personal or local or confined to any one country. We have an authority in the International Committee against which such objections do not hold, and it seems only fair to accept their verdict, leaving it to them to make changes when, after due deliberation, they consider changes advisable.

Schereschewsky in 1909 cultivated the organism of syphilis from the human lesion, but it now seems probable that his culture was contaminated and that *Treponema pallidum* was first grown in pure culture by Noguchi[1] in 1911 from the testicles of a rabbit and was first obtained in pure culture from human le-

sions by this same authority[2] in 1912. Muhlens[3] and Hoffmann[4] also claim to have grown *Treponema pallidum* in pure culture, but base their claims entirely upon the morphologic characteristics of the organism.

It was confidently believed that the discovery of the organism of syphilis and methods of cultivating it would give information concerning syphilitic antibodies and processes of immunity which might prove of value from a curative or prophylactic standpoint, especially so after Kolmer[5] and Zinsser and Hopkins[6] had shown that culture organisms were agglutinated in fairly high dilutions by the sera of rabbits treated with culture organisms. Unfortunately much of the information obtained has been of a negative character. One of the early developments was to the effect that the Wassermann reaction is not a specific reaction and that it depends upon lipotropic substances present as metabolic products of syphilitic processes. An unexpected result of the cultural methods was the discovery that the characteristics of the organism are materially changed by growth in an artificial medium, and from a standpoint of immunologic reactions as well as infectivity for animals, there seems to be little relation between them. Except that Noguchi carried the strain back to animals before it had become thoroughly adapted to a test tube existence, it would seem doubtful if there were a common identity. In studying the culture organism, it was also shown that in addition to agglutinins, treponemacidal substances analogous to bactericidal antibodies were also developed. By cross agglutination and absorption experiments, it has been shown by Zinsser[7] that treponemata cultivated from various sources are related in group reactions and that there is a marked variation in the agglutinability of the several strains studied. This might serve as a further argument in favor of the strain theory with reference to Treponema pallidum. This work at first seemed very encouraging, but upon further investigation was shown to have apparently no practical bearing upon the subject of syphilis. These rabbits which were immunized with culture pallidum developed agglutinins and lysins against culture organisms, but no such reactions against pathogenic organisms could be determined. It was also shown that the sera of syphilitic rabbits developed no immunologic re-

actions against either the pathogenic or culture pallidum. Nakano[8] injected rabbits with a heat-killed culture and with the resulting serum, obtained agglutinations with a culture organism in a dilution of 1:10 to 1:70. Prior to this time a number of European observers had attempted work of this same kind, but due to the fact that they had only organisms from human or experimental syphilis, it was impossible on account of technical difficulties to obtain any very definite results. Kolmer[5] reported that the sera of rabbits injected with living and killed cultures, agglutinated the cultured organism in dilutions as high as 1:1,280. Normal rabbit serum did not agglutinate as low as 1:20 and nineteen syphilitics in various stages and ten nonsyphilitics did not agglutinate in the same dilutions. Feeling later that these dilutions were too high, a new series of investigations was carried out by Kolmer, Broadwell and Matsunami.[9] In this work, as before, a culture organism was used. Their findings were that the sera of normal individuals and those suffering with diseases other than syphilis, did not agglutinate in dilutions of 1:5 or higher. In primary syphilitics only traces could be found. It could be found in secondary syphilis in dilutions of from 1:5 to 1:20 in about one-half of the cases, and in tertiary and nervous syphilis it was evident in dilutions of 1:5 or higher, in 84 per cent of cases examined. It did not appear as soon as the Wassermann reaction. It may be present with a negative Wassermann reaction and vice versa. Kolmer and Broadwell[10] found that in no stage of syphilis can there be demonstrated any treponemacidal action of human serum for culture organisms and that there is no relationship between the occurrence of cutaneous hypersensitiveness to luetin and the presence of agglutinins or complement-fixing antibodies. They conclude from this work that the anaphylactic luetin test can in no way be regarded as indicating a resistance to Treponema pallidum. It would therefore appear that the failure to produce in animals an active immunity to syphilis would indicate that "the lytic type of immunity is absent in syphilis or at least plays but a minor role in this infection." Neisser and Bruck[11] hold a similar opinion and state that there is no true immunity in syphilis. With reference to the above work, Zinsser[7] states: "We have tried with a considerable number of cases and found that al-

though the sera of tertiary syphilitics will sometimes agglutinate a little more highly than will the sera of normal individuals, yet many patients suffering from nonsyphilitic diseases, agglutinated as highly and almost regularly as did the syphilitics." He further states that it is not possible to immunize rabbits against syphilis by injecting locally or intravenously, either living or dead cultures or dead pathogenic organisms, and the sera obtained from animals has no effect upon pathogenic organisms *in vitro* and can not be used to confer a passive immunity upon another rabbit. We are, therefore compelled to believe that during the course of this disease, there is no proper antibody formation as we know it in bacterial diseases and that as a result, immunity to syphilis in the common acceptance of the term, does not exist. As a result of several accidental laboratory infections, it has been shown that passage through the rabbit in no way reduces the virulence of the organism for man. Metchnikoff attempted to attenuate the organism by passage through monkeys and in that way obtain an immunity, but his results were in no way conclusive or convincing. It may be said that the prospects for obtaining a prophylactic or curative vaccine or serum for syphilis in the immediate future are not very promising.

We do not then know the nature of the resistance which seems to be established in the syphilitic. So long as the infection exists, there seems to be immunity to a new infection. It seems a most plausible hypothesis that in the superficial layers of the epidermis and the true skin, certain cells are stimulated to react by the presence for the first time of Treponema pallidum, but that following this initial lesion (which we must admit is a most beneficent act upon the part of nature in the way of a danger signal), this power of reaction, or attempt at defense is lost and that following generalization of an infection, there is a "complete failure of the tissue cells to react to the virus, a sort of tissue indifference or anergie;" and as a corollary it would appear that the presence or absence of a new infection is in no way to be predicated upon the appearance of a second initial lesion. The question then arises as to whether or not it might be possible to graft a second and possibly a more virulent strain of syphilis upon an existing infection but, of course, without a pre-

liminary initial lesion. From all the information available by way of analogy, clinical evidence and animal experiment, I am inclined to believe that such a thing is not possible. Finger and Landsteiner[12] as a result of monkey inoculations, conclude that immunity in syphilis is only relative and can be overcome by the injection of infective material in considerable quantities and that the resultant lesion manifests itself in harmony with the stage of the disease at that time present in the infected individual. In such work it would seem to be rather a difficult matter to differentiate accurately between traumatic lesions or ordinary infection; as compared with true syphilitic lesions due to the original infection; bearing in mind the susceptibility of the skin in syphilitics. It is very generally accepted that other protozoal infections are not susceptible to such superinfections. Treponema pallidum from a physiologic and therapeutic standpoint has characteristics in common with the trypanosomes and piroplasmones, one of them being the apparent immunity to a second infection so long as the first is still existent. Levaditi maintains as a result of his experimental work that animals suffering from spirillary infections are immune to new inoculations. The known facts upon superinfections may be summed up as follows: A second infection with a second initial lesion may occur for a period varying from the first twelve up to the twentieth day following original infection and after this period up to the time of cure, superinoculations will not result in an initial lesion.

Cases have been reported by Fordyce[13] and Hazen[14] where surgical assistants have punctured the skin with an infected instrument and while under close observation, developed generalized syphilis without an initial lesion. This would seem to indicate that the initial lesion is not to be considered as a necessary phase of the disease and that immunity to further initial lesions, either from within or without, appears following generalization and not as a result of the initial lesion. Some explanation is certainly to be desired of the large number of cases we are now seeing which give no history of any initial lesion. Treponemata frequently pass into cells or may be taken up by phagocytes, in which latter case lysis can not be observed and the organism continues to exist as long as could be expected under the untoward circumstances which must necessarily surround it

while under observation. It is not believed that phagocytosis plays any part in the immunity processes of syphilis.

It has been generally taught and believed that it is not possible to contract a syphilitic infection through the unbroken skin or mucous membrane. Without the evidence of the microscope, it would seem to be a rather difficult matter to say that minute traumatic abrasions are not present upon the epidermis. There would seem to be no reason why this organism should not pass into one of the squamous cells of the mucous membrane as into the cells of the liver or pancreas or other organ, and especially so where desquamation has just taken place. The possibility of infecting the rabbit by applications of infective material to the apparently unbroken mucous membrane of the vagina, has been demonstrated.[15]

Racial immunity does not exist, though it has been claimed by some writers that all races are not affected alike. In view of the vastly different climate, altitude, diet, degree of temperance, or intemperance, physical exercise, degree of sexuality and general environment which may exist, such a statement would seem very possible. Quite probably, according to Fordyce, the Hebrew race owe their supposed immunity to circumcision, a high degree of sexual morality, and early marriage. Neisser[16] found few visceral or nervous lesions among the Malays though the cases were poorly treated and tertiary lesions were common. The question of strains should be considered in explaining such conditions. While it is a common statement that in the tropics, Europeans suffer more severely than the natives, such statement is open to question and might be a subject for extended investigation.

Colles' and Profeta's laws are only mentioned as examples of exploded theories and discarded beliefs. The first held that mothers who had borne syphilitic children could not be infected by the child or otherwise, on account of an acquired immunity to the disease. The second was to the effect that children born of syphilitic mothers have an immunity. It is now known that these individuals who were supposed to be immune, were, in many cases, infected but without external manifestations and for this reason could not develop an initial lesion so long as they were uncured.

Probably no word in connection with the description of syphilitic processes is more misunderstood and abused than the expression "latent syphilis." As it is ordinarily used, it does not refer to a condition where, as a result of immune processes or loss of pathogenicity, the disease is being held in check and is truly latent. On the contrary, in the vast majority of these cases, it is only syphilis without obvious external manifestations and frequently is accompanied by active pathologic involvement of the aorta, the meninges, the brain, or cord. There seems to be a demand for a term with which to designate this class of cases and the word "latent" is misused to this end. It would seem that a better designation might be found, such as syphilis without external manifestations, nonmanifest syphilis, repressed syphilis, concealed syphilis, or endosyphilis. My preference would be for the last term. A truly latent syphilis would give a consistently negative Wassermann reaction and would be without manifestations or active pathologic processes in any organ. In the absence of a history, the diagnosis of such a condition would seem to present elements of difficulty.

While in all probability the experimental transmission of syphilis to the lower monkeys was performed by Klebs about thirty-seven years ago, yet the first successful animal inoculation about which there could be no question, was made by Metchnikoff and Roux[17] in 1903 upon a chimpanzee. The confirmation of the diagnosis was made upon the basis of a characteristic initial lesion and secondary manifestations. Other experimenters followed, and in 1906, Bertarelli obtained a syphilitic keratitis in the rabbit and the following year Parodi[18] for the first time obtained a syphilitic orchitis in the same animal. In the meantime, Schaudinn's discovery of the organism had given an immense impetus to the work and many investigators had become interested.

In spite of statements to the effect that syphilis in the rabbit is a purely local affair and not accompanied by the same generalization and results of generalizations noted in man, I, as a result of published[19] and unpublished work, am not at the present time willing to accept this view. Adult rabbits may be infected by intravenous inoculations without the appearance of an initial lesion and, after the lapse of six weeks, are not readily

susceptible to initial lesions from testicular injections. Lesions are to be found in many organs and from a rabbit infected by way of the testicle, it is possible to transmit the disease with the blood or emulsions of various organs. Experimental attempts at super-infection were carried out according to the following plan: Rabbits were first successfully inoculated with a strain not producing choroidal involvement and following this, repeated injections were made intratesticularly, subcutaneously, intraperitoneally, intravenously, etc., but in no case was choroidal involvement obtained during the active phase of the disease. It would appear that immunity in the rabbit is the same, no matter by what means inoculated. It is true that one does not see in the rabbit so many diverse pathologic manifestations as are observed in man, but this is due to failure of the generalization to produce pathologic lesions rather than to a lack of generalization.

It had been suggested for many years that paresis and tabes were frequently, if not always, of a syphilitic nature. Due to their variation from syphilis as it had always been known, an attempt was made to explain the relationship designating these conditions as parasyphilitic in nature, without having any very exact comprehension of the term. It has been quite generally held of late that patients suffering with tabes and paresis have been infected with a type of syphilis which is not inclined to cutaneous manifestations and in this connection the work of White[20] at the Massachusetts General Hospital, is most interesting. Of five hundred tabetics he found that 18, or 3.6 per cent only, had exhibited cutaneous manifestations, and of 178 paretics, only 2, or 1.12 per cent, had shown cutaneous manifestations. These results are in keeping with the findings of other investigators. In 1913, Nichols[21] noted the varying tendency of strains of syphilis to attack different tissues in the rabbit and the following year[22] made the statement following considerable experimental research, that there are different strains of Treponema pallidum, and that these strains have among other characteristics a varying degree of invasiveness as is shown by their predilection for attacking different tissues in the rabbit. It remained for Noguchi and Moore[23] to demonstrate the presence of Treponema pallidum in the brains of paretics and the spinal

cords of tabetics. Later Noguchi,[24] Berger,[25] and Nichols and Hough[26] transmitted the disease from the paretic brain to the testicles of a rabbit and obtained a syphilitic lesion. In all these cases the inoculations were made from material obtained after the death of the patient.

The next step in this work was taken by Wile[27] when he secured portions of the cortical substance of six living paretics and injected the resulting emulsion into the testicles of a rabbit after dark-field examination had shown the presence of treponemata. The rabbit presented evidences of syphilitic involvement of the testicle in a little less than the usual time and the infection was transmitted to other rabbits up to the fourth generation. These strains were also studied in culture. Wile concluded that rabbits are easily infected with syphilis by paretic brain material and that such strains are distinctly more virulent and have a shorter incubation period. Noguchi and Nichols and Hough, on the other hand, arrived at the conclusion that rabbits are not easily infected with paretic strains, and that when infected, the incubation period is longer and such strains are difficult to maintain in culture. The latter conclusions would seem to be more in accord with clinical evidence. The syphilitic secondaries do not appear so characteristically in the rabbit as in man or even so much as in the chimpanzee. The rabbit is not so closely related to man, and therefore a question might be raised as to the degree of analogy to be accepted in the interpretation of the results of experimental work. The rabbit, however, suffers involvement of various tissues, as will be shown, and is a fairly satisfactory subject and is easily handled and obtained. The site of election for experimental inoculation is in the testicle. An initial lesion may be produced in the eye and occasionally in the eyebrow and epidermis of other portions of the body. It is also possible to inoculate by injections in the different tissues or intravenously, and by such methods, in adult rabbits, general syphilization will ordinarily take place but without the appearance of an initial lesion. The initial lesion manifests itself usually in from three to eight weeks, but has an average of about thirty-five days, as determined by palpation. It may be anything from a slight edematous swelling of the testicle, to a large indurated lesion with central mucoid degenera-

tion or necrosis and this may later present itself as an external ulcer. The organisms may be found in great numbers when the lesion first develops, especially if there be a quantity of serous effusion. The disease becomes generalized rapidly as has been shown[19] by the successful transfer from the blood of an inoculated rabbit, more than two weeks before the initial lesion had become manifest. Evidences of pathologic changes have been noted in the nervous system, liver, kidneys, blood vessels, eyes, etc. Alopecia and paronychia are fairly common, and involvement of the mucous membrane of the nose was observed frequently in one strain which was studied for a number of years. The animals may become emaciated and die apparently as a result of nervous or other involvement. It is believed that the general tendency is to recover.

In transmitting from human lesions to animals, an initial lesion containing by preference many active treponemata, is selected and well cleansed with physiologic normal salt solution. A capillary pipette containing a drop of the above solution either with or without one per cent sodium citrate, is used to collect some of the chancre juice obtained by expressing the sore. It is then mixed in a watch crystal with 2 to 4 c.c. of the above solution and after cleansing the scrotal skin is injected into the substance of the testicle by means of a hypodermic syringe. When transferring from one rabbit to another, the capillary pipette prepared in the same manner is forced into the body of the testicle and the collected serum mixed and injected in the same manner. When it is desired to transfer from an old rabbit lesion, it may be necessary to remove and emulsify a part of the testicle and inject in the same manner. Strict attention should be given in order to obtain an aseptic technic and not more than one c.c. should be injected into a testicle. Frequent puncture of a testicle for diagnostic or other purposes may, as the result of hemorrhage, trauma, or secondary infection, so alter the appearance of the organ and interfere with the development of the lesion, as to lead to an incorrect conclusion concerning the type of lesion. In following a first transfer to a rabbit, it is advisable to make repeated punctures in order to avoid the possibility of the lesion passing unrecognized. Having obtained some information as to the type to expect and a line

upon the incubation period, it is then preferable to depend upon palpation for the recognition of the lesion in subsequent transfers. It is believed that this is the only correct standard for determining the characteristics of an initial lesion as well as its incubation period. Failure to use such methods might explain some of the contradictory reports of various investigators. It is also necessary to use adult animals with well-formed testicles and to keep them under favorable conditions with respect to sunlight, ventilation, and cleanliness. It is needless to say that no operation involving serious pain or discomfort to the animal should be undertaken without a general anesthetic and that following any serious or untoward condition, the animal should be killed promptly and painlessly.

As a result of over six years' work, begun by Nichols,[21, 22] and carried on by Reasoner[19] they were able to show among twenty strains studied, several with characteristics sufficiently obvious to serve as a means of ready identification and differentiation. Three types were observed with characteristics sufficiently predominant to distinguish them one from the other, despite the normal variation from rabbit to rabbit. Other strains occasionally showed less obvious characteristics when studied in a series of rabbits. The differences observed are based upon the following characteristics described more in detail in a previous report.[19] (a) Length of incubation period which may vary from twelve to sixty days. In four strains studied in a number of generations, averages of forty-two, thirty-nine, thirty-four, and thirty days, respectively, were obtained. (b) Type of chancre which may vary all the way from a slight edema scarcely palpable in some strains, to a greatly enlarged and indurated testicle eventuating in a necrotic center and external ulcer. (c) Duration of lesion. The averages in the four strains mentioned were 40 days, 108 days, 94 days, and 33 days, respectively. Obviously the strains accompanied by a considerable amount of induration remained in evidence longer. One strain in no case remained palpable more than 50 days, and another in no case remained palpable less than 60 days. (d) Only one strain of the four developed an external lesion and that in 50 per cent of the rabbits. (Later statistics decreased this incidence to 38 per cent.) (e) Extension to the opposite testicle was observed in

only one strain where it was encountered in 10 per cent of the animals. (f) Choroiditis first described in the rabbit by Nichols and Greene[22] was seen in only three strains of twenty, and varied from 70 to 95 per cent in these three strains. This condition was seen in two undoubted strains of nervous syphilis, obtained by the injection of spinal fluid from patients so affected.[28, 29] (g) Paronychia was observed several times in three of the four strains carefully studied. It is not in any way a constant manifestation. (h) Involvement of the eyelids, penile and nasal mucosas and nasal bones was observed in only one strain; a nervous strain believed by Nichols to have unusual invasive power. (i) Alopecia in a greater or less degree is a common occurrence and not believed to be specially characteristic of individual strains. Both Noguchi and Zinsser mention a strain seen by them which presented a variable type of initial lesion; at one time soft and edematous, in other rabbits enlarged and indurated. We have not encountered such a condition. Pericorneal injection progressing occasionally to keratitis, was observed more frequently in three of the strains mentioned above, while in the fourth, known to be a mild strain in man, it was not observed as a result of testicular injections. If, however, intravenous injections were given at short intervals after the appearance of the initial lesion, it was seen more often and in more severe form than in either of the other three strains. If the intravenous injections were delayed for a period of several months, no results were obtained. While choroiditis was a fairly constant manifestation in the first three strains following any form of inoculation, yet in the last strain mentioned above, it was not possible to produce it in any one of a large series of rabbits by as many as ten subsequent intravenous inoculations of rich emulsion. It would, therefore, seem that the choroiditis noted in some strains was produced as the result of a definite tendency upon the part of the strains in question and was not due to the persistent attack of an indifferent Treponema.

Generalization in the rabbit may take place before the lesion is palpable in the testicle and in a small series of rabbits, has been shown to be present as early as twenty days after inoculation.

We have not yet been able to form final conclusions as to the relation existing between involvement of the nervous system in man and the same condition which we repeatedly have found to be most characteristically present in the rabbit. This is due, possibly, to the fact that a sufficient number of strains have not been studied over a long period of time and in a relatively large number of rabbits. The evidence obtained from the study of over two hundred and fifty rabbits is strongly confirmatory of the belief enunciated by Nichols, that a strain producing nervous syphilis in man, will have a tendency to produce a choroiditis in the rabbit. The eye of the rabbit is so different from that of man, that some difficulty will be experienced in interpreting results even by one familiar with the use of the ophthalmoscope. One must also be careful that the peculiar arrangements of pigment do not lead to erroneous conclusions. I am strongly inclined to believe that Strain No. 10^{19} has a definite predilection for the circulatory system of the rabbit. It has not seemed possible to draw any conclusions from the type of the initial lesion of the rabbit, which under favorable conditions usually varies only within certain limits. For instance Nichol's No. 5 strain[22] which was obtained from the spinal fluid of a neurorecidive, is of a distinctly different type from my No. 19 strain[29] which was obtained from the spinal fluid of a man who, despite a fair amount of interrupted treatment, died of cerebral syphilis at the end of ten months from the time of contracting the infection. Noguchi has described a malignant strain of syphilis having a somewhat similar type of initial lesion to the No. 19 strain.

It is a logical question to ask what may be expected from the further study of experimental syphilis. It is perhaps not too strong a statement to say that we have gained much of the absolute knowledge we have of the disease. The plaything or toy of one generation of scientists often becomes the keystone of the most important structure of the next generation. We have not yet solved a number of the problems connected with a comprehensive knowledge of this disease, but it is possible that much of the required information has been obtained and only awaits the intelligence able to interpret or the touch of the hand able to form and solve the equation. It may be that the future will

add the additional facts necessary to correlate and combine and understand that which we have already obtained. Many phases of the subject of experimental syphilis have engaged the attention of different investigators. A few of the questions involved are given below. In the seven years' Army Medical School work, initiated by Nichols and carried on by myself, the first nine were under consideration.

1. How soon does generalization take place and where? Over how long a period does it last?

2. A further solution of the strain question, to include, if possible, the development of a certain means of recognizing strains early in the course of the disease. Is it a matter of virulence or of a predilection for certain tissues?

3. Is there a strain having a definite tendency toward blood vessel involvement?

4. A solution of the problem sometimes designated as "Protozoal immunity" and the many questions dependent upon it. Is it possible to develop a vaccine or immune serum? Is it possible to transfer immunity without the disease? Is the syphilitic really immune to further infection or is this condition only apparent?

5. The relationship, if any, existing between syphilis and yaws.

6. The relationship of the initial lesion to the disease as a whole. What are the conditions under which it may be absent or present only in a modified form?

7. Is the disease often contracted through apparently unbroken skin or mucous membrane?

8. Methods of prophylaxis of the disease.

9. Are the manifestations of syphilis more malignant in the tropics than in temperate climates?

10. The development of a culture method which will not alter the organism so far as pathogenicity and serologic reactions are concerned.

11. The possible synthesis of other chemical compounds which may be more effective than arsphenamine. This, of course, can only be accomplished by the aid of animal experiment.

General Pathology

After the treponema is successfully implanted it begins to multiply, as shown by Levaditi and Gamanouchi, and to call forth changes in the cutaneous vessels, and to enter the blood and lymph streams. It has been shown by Neisser[30] that the bone marrow, spleen and satellite lymph nodes contain the organism by the time that the chancre is clinically evident, which point is an excellent argument against excising the chancre as a routine therapeutic measure.

As the chancre develops, a peculiar reaction upon the part of the body is also forming. At first it is so feeble that the patient is liable to reinoculation. In animals it has been found that superinfection is possible if made within eight days before the evolution of the primary sclerosis. Multiple chancres in the human being may result from multiple simultaneous inoculations, from autoinoculation, or from a separate and later inoculation. Superinfection lesions do not develop in the typical manner; their period of incubation is shorter than usual, and when developed, their clinical characteristics resemble those of the stage of syphilis that the patient is in at the time, papular at the time of the secondary, and ulcerative at the time of the tertiary. They are the expression of an altered tissue reaction.

It is well known that the first or initial lesion is usually solitary, but that during its development the treponemata are actively engaged in multiplying in various portions of the body as mentioned above. Then there occurs a sudden dissemination of them, a septicemia as it were, which is generally held to be limited to the superficial structures of the body, notably the skin and mucous surfaces. In the due course of time, just how long is still unknown, their presence calls forth a reaction on the part of the tissues in which they are lodged, and this reaction is best known in the form of the secondary syphilides of the skin and of the throat and mouth. However, it is becoming more and more certain that at this time many of the deeper structures are invaded. As an example of this it is only necessary to call attention to the recent work showing that the central nervous system is involved in a high percentage of cases at this early date.[31] Fortunately the resulting lesions, which must be considered as the

expression of tissue reaction to the treponema, are usually comparatively mild in character and do not result in the destruction of tissue.

During the course of late syphilis the lesions are localized, are fewer in number, and there are fewer organisms present, but ulceration usually results. This difference upon the part of the bodily reaction is not believed to be due to a change upon the part of the organism, but to a change in the tissues of the body to which the term "allergy" is applied. In the early stages where the organisms are numerous the host is refractive, but in the later stages when the organisms are comparatively few in number the tissues are more susceptible and readily undergo necrosis. The so-called malignant syphilis is simply due to an early allergy upon the part of the body of the victim.

These processes of immunity are subject to modification under treatment. Where treatment is intensive and yet not sufficient to complete a cure, the anaphylactic stage may be hastened, and specific treatment given early in the course of the disease may tend to produce relapses of increased local intensity. In this connection we may note that it is claimed by some that the use of arsphenamine has changed the course of the disease, and that when it is not given in sufficient quantity to sterilize the patient, tertiary lesions may appear much earlier than when the disease is permitted to run its natural course with the production of a natural defensive mechanism.

The relationship of trauma to syphilitic lesions is now pretty generally recognized. The query arises whether the organism was present at the site of injury or was later deposited at that site. As bearing upon this point Pasini has demonstrated treponemata in an atrophic and pigmented spot two years after the involution of a papular syphilide, while Hoffmann had demonstrated them in the scar of a chancre long after the disappearance of the primary focus. The so-called chancre redux or relapsing chancre is interpreted by many as being the result of organisms which have remained *in situ,* rather than as a superinfection. Neisser has shown that the organisms may be present in the skin without calling forth any tissue inflammation.

Studies upon the infectiousness of the blood by Uhlenhuth and Mulzer[32] have supplied us with the following data:

Primary stage		*Secondary stage*		*Late stage*	
No. of cases	Those positive	No. of cases	Positives	No. cases	Positive
19	16	36	27	15	2

The above facts are in accord with the clinical observations that the blood of luetic individuals is infectious during the primary and secondary stages, but that this infectiousness decreases as the disease becomes older. Kraus[33] has suggested that the febrile attacks that sometimes accompany syphilis may be due to a sudden dissemination of the treponemata, an analogy being found in either leprosy or trypanosomiasis.

Fordyce's[34] article contains an elaboration of the above views, and it is to this article that I am much indebted.

Syphilis has certain general effects upon the general system. As is well known the number of the red blood cells and the amount of hemoglobin is sometimes decreased. In the European clinics considerable stress was formerly placed upon this fact as a diagnostic sign, particularly in women. In America there does not seem to be so general an anemia, but nevertheless it does often occur. The administration of mercury to a syphilitic frequently causes a marked drop in the quantity of the hemoglobin, and this was considered by Justus[35] to be characteristic of the disease. I[36] have definitely shown that an increase in the number of leucocytes not infrequently accompanies the early and sometimes the late stages of the disease. The administration of either mercury or arsphenamine causes a rise in the actual and relative number of the small mononuclear cells, although the same is true of nonsyphilitic subjects.

As a general rule there is very little evidence of kidney irritation, although at times there may be a trace of albumin in the urine. A true nephritis is usually due to either the administration of mercury, to a true gummous formation, or more rarely to amyloid degeneration.

The flow of gastric juice is sometimes markedly altered during the florid stage, and it is not unusual to find acute, but temporary, gastric disturbances during this period. This may be due to an eruption upon the mucous membranes, a true gastritis, or to a disturbance in the quantity of the secretions.

Histologic Pathology

Fordyce[37] pertinently remarks: "The predilection of syphilis for the vascular system is noted almost from the inception of the disease in the involvement of the cutaneous vessels at the point of inoculation. Here the pathologic process consists of an endarteritis, later a periarteritis with characteristic inflamma-

Fig. 2.—The section from which this photograph was made was taken from the edge of an early chancre. Notice the thickening of the blood vessel walls and the perivascular infiltration. (Collection of Drs. Fordyce and MacKee.)

tory infiltration * * * A study of the pathologic anatomy of syphilis shows that fundamentally the reaction is on the part of the connective tissue elements, the labile constituents coming into play only secondarily. The chief cells are the lymphocytes and plasma cell, the latter believed to be a derivative of the for-

mer and an antecedent of the fibroblast." No matter at what stage a syphilitic reaction develops, it is essentially a granuloma having its origin in the perivascular lymph stages. This is true of all forms and of all stages of syphilis, with one exception, namely, the primary syphilis of the heart muscles, as will be pointed out in the section devoted to that organ.

As will later be pointed out in more detail, in chancre the chief changes are in the cutis, and at the onset are characterized by an early endarteritis with a later periarteritis, with a characteristic coat-sleeve infiltration around the affected vessels, the cells consisting of small mononuclears and plasma cells. The endothelium of the capillaries is swollen and proliferated. Rarely giant cells may be found. In the older lesions there is a massive infiltration, so that the individual vessels are often extremely difficult to detect.

In the secondary lesions the lesions are very similar to those just described, except that a massive infiltration is rare; the infiltration while heavy, can usually be seen to surround blood vessels. In general the vessels are thickened and the endothelium swollen and proliferated. A panarteritis is common. Giant cells are more common than in chancre, but are none too frequently encountered.

In the late lesions there are two distinct types of involvement. With the exception of the heart muscle the involvement is always interstitial and always begins around the blood vessels. This is especially noticeable in the various glandular organs and also in the lungs. While the beginning is the same, the later course of the two processes is markedly different. In one type there is the formation of numerous miliary gummata that run in bands along the interstitial tissue and which never completely necrose, but which are soon replaced by scar tissue, and at times eventually by calcareous deposits. This is the type that gives rise to the cirrhosis of the various organs. In the other type one or more frank gummata form. These begin just as do the other syphilitic processes, but the tissues are friable and necrosis follows at some later date, sometimes within two weeks and sometimes not for nearly two years. These gummata are large and the ulcerative processes always seek the path of least resistance and eventually ulcerate to the surface or into

some bodily cavity. At times they may be arrested before any extensive destruction has taken place, but this is by no means always the rule. Once destruction has occurred, healing is usually slow because of a deficient blood supply. Eventually, however, these lesions will heal by the formation of scar tissue. It should again be emphasized that no matter where a late syphi-

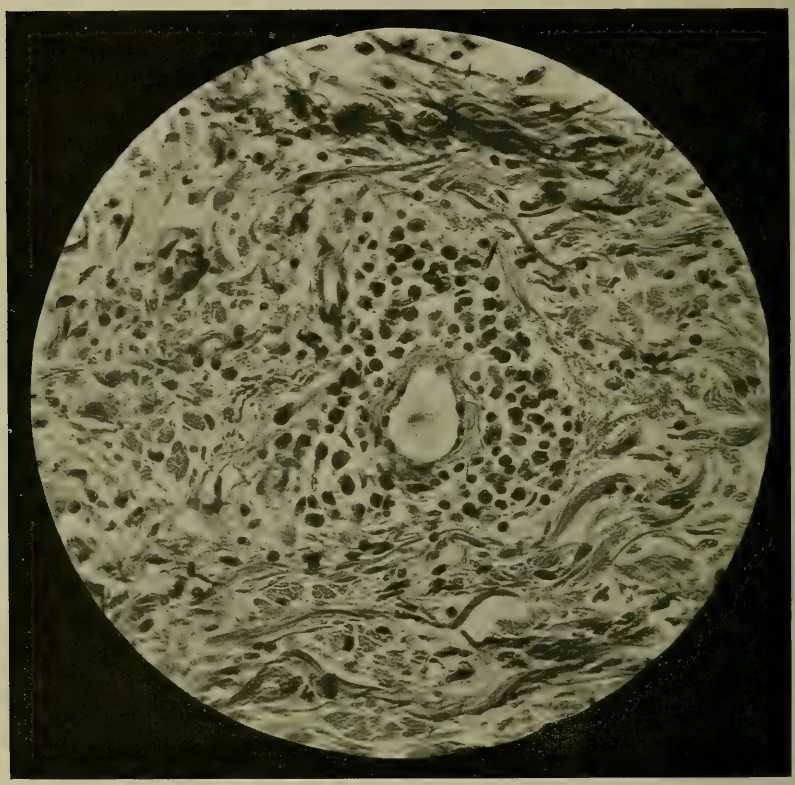

Fig. 3.—This illustration shows the perivascular infiltration occurring in a secondary skin lesion. The plasma cells show very distinctly. (Collection of Drs. Fordyce and MacKee.)

litic process occurs, whether it be in the skin, testicle, brain or liver, the essential process is the same.[37]

To the above statement there is, however, one notable exception. As will be pointed out more in detail in the section dealing with disease of the heart muscle, in certain instances the

inflammation is not necessarily interstitial, but may primarily attack the muscle fibers.

Recently Warthin has written a very interesting paper which should be read by any one interested in the pathology of syphilis. Warthin points out that microscopically the inflammation of syphilis is characteristic, and that the condition can fre-

Fig. 4.—Even in paresis the brain vessels show the same "coatsleeve" infiltration as is found in the earlier lesions. (Collection of Dr. John A. Fordyce.)

quently be recognized only microscopically, certainly not by the naked eye. In many instances there is but a mild degree of the characteristic perivascular infiltrate, not sufficient to call a granuloma, and yet the treponema can frequently be recognized by the Levaditi stain.[38]

Autopsy Findings in Syphilis

From a study of the gross anatomy Symmers found in a study of 4,880 autopsies performed at the Bellevue Hospital evidence of syphilis in only 314 cases, or 6.5 per cent. Lesions of the skin were found 106 times, hyperplasia of the lymph nodes 20 times, bone lesions 48 times, orchitis in 67 instances, lesions of the respiratory tract 35 times, lesions of nervous system in 112 cases, syphilis of the liver 105 times, aortitis in 175 cases, aneurysms in 45 cases, gastric ulcer once, and the intestines were involved six times.

In marked contrast to these findings are those of Warthin, who also made a careful histologic examination of all tissues, and he reports that in 750 autopsies performed at Ann Arbor during the last ten years, evidence of syphilitic infection was found in no fewer than 300 cases. Warthin points out that the gross anatomic study as done at the autopsy table will not establish the diagnosis of syphilis in the majority of the cases, a view in which I most heartily coincide.[39]

Recently Graves has extended his original report of postmortem Wassermanns and has found that the postmortem reports confirmed the antemortem reports in 97 per cent of the cases. This may be of value in medicolegal cases.[40]

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CHAPTER IV

CLINICAL COURSE

Syphilis is frequently compared to the various exanthemic fevers, and in some respects this comparison is justified, for there is a definite incubation period, followed by a systemic disturbance with a more or less generalized rash. But here the similarity ends, for barring the complications, the exanthemata end promptly, while the infection of syphilis is essentially chronic, usually enduring for years.

It has been customary to divide the course of syphilis into four stages, the primary, secondary, tertiary and quaternary or parasyphilitic. A number of excellent observers, including George Henry Fox,[1] consider that this is wrong, and that syphilis has but two phases, early and late. The term parasyphilitic should be dropped entirely, since it has been conclusively shown that the so-called parasyphilitic lesions are truly syphilitic.

Primary Stage

The incubation period varies from three to six weeks, with a probable average of about four. Hutchinson[2] has always contended in favor of a long period, and feels that five weeks is about the average. He quotes a number of interesting cases to support his beliefs. Andrews[3] states that animal experimentation has shown that in apes the period is from three to four weeks.

The primary lesion is known as the chancre and may appear upon any portion of the skin or mucous membranes, although usually upon the genitals. In exceptional instances no chancre is seen. However, as a general rule close examination will reveal the presence of a lesion in an obscure location, as in the urethra or upon the cervix. At times, too, the initial lesion may be so small and insignificant as to escape notice.[4] When there is no chancre the condition is spoken of as "syphilis d'emblée" and has been carefully considered by both Almkvist[5] and Gott-

heil,[6] both of whom consider it extremely rare. The former believes that there are only four cases upon record, those of Jullien, Waelsch and Bettmann, which are conclusive. All four of them occurred in physicians who cut or pricked themselves during an operation. Since this time both Fordyce[7] and I[8] have recorded similar cases in which there could be no doubt. In addition to these the literature contains about twenty-five cases in which no initial lesion was found. However, neither Almkvist nor Gottheil can accept these instances. Lane[9] has reported six cases of "syphilis d'emblée," several of which appear authentic. I feel, therefore, that while these cases are undoubtedly very rare, still they are not as exceptional as Gottheil would have us believe.

In addition to the chancre the primary stage also includes the local lymph node involvement, which is usually quite evident. Ordinarily this develops in from two to three weeks after the appearance of the initial sore. The glands in connection with an extragenital chancre are usually much larger than those from a genital one, just why it is difficult to say, unless it be because the chancre itself is usually of rather more marked proportions.

In the preceding chapters I have called attention to the fact that it has been shown by Neisser that the treponemata can be found in various lymphatic structures by the time that the chancre has manifested itself. As a general rule during the periods of incubation and of the subsequent development of the chancre there is but little general disturbance. However, at times even for several weeks before the chancre appears there may be marked systemic disturbances. Recently I saw a physician for a chancre of the finger, who had lost over twenty pounds in weight and who had felt very ill for a month before the initial sclerosis manifested itself. I have seen several other cases in which the general health suffered greatly while the chancre was present and before the rash appeared. These disturbances consist of malaise, loss of weight and strength, and general lassitude.

The Early Stage

The secondary or early stage is due to the widespread dissemination of the organisms, a septicemia, with most of the lesions su-

perficially located in either the skin or mucous membranes. This stage usually appears in from four to twelve weeks after the initial lesion has first manifested itself. Its most prominent characteristic is usually the rash, which may assume any one of many forms. In addition there is often a pharyngitis and the so-called mucous patches of the mouth and lips, which are simply modified papules. Condylomata or moist papules may appear early, but usually do not erupt for several months. Some degree of alopecia occurs in about 10 per cent of all secondary cases. Arthritic pains occur in a large percentage of all patients. Headaches are common, and may denote early involvement of the central nervous system, or may be simply signs of a general toxemia. A more or less general glandular enlargement occurs in about 50 per cent of the whites, but in a much higher proportion of negroes. Iritis is not infrequent. In addition there are frequently certain general disturbances. A moderate amount of fever is found in many cases, especially in patients with pustular lesions. Bronchitis is frequent and laryngitis not uncommon. Some patients show marked digestive disturbances, and I have seen cases in which there was persistent vomiting for weeks. Acute yellow atrophy of the liver has been reported by many observers, and some jaundice is not infrequently seen. The spleen is often enlarged. There is at times some anemia, usually of the secondary type, and the leucocytes are often increased. However, the lesions may be ulcerative or gummous from the first, due to the resistance of the patient and not to any special virulence on the part of the treponema. As a general rule the early manifestations disappear even if untreated, but both the mucous patches and the condylomata are often very stubborn. In White's[10] series of 505 secondary cases cutaneous manifestations were seen in 225 patients, mucous patches in 226, pharyngitis in 193, iritis in 25, condylomata in 41, headache in 133 and alopecia in 47.

Following the secondaries there often is a latent stage of varied duration, sometimes two months and sometimes ten or even more years, but usually about two to three years, before the deeper lesions begin to appear. This stage is called the early latent period. In many instances before the appearance of the late lesions there may be a recrudescence of the secondaries,

either mild or severe. Such a recurrence undoubtedly takes place in at least 20 per cent of all syphilitics who neglect treatment. Mucous patches and condylomata are especially apt to develop during this period, and various varieties of superficial cutaneous rashes are far from rare. Associated with such outbreaks there may be any of the other signs of syphilis already mentioned, and in addition some deeper lesions are not uncommon.

The Late Stage

The tertiary or late stage consists of gummous processes, usually localized to some particular organ, although many may be affected at one time. Either deep or superficial structures may be attacked, but the treponema has a marked predilection for nervous and arterial tissues, bone, skin, liver, testicles and adrenals. Any organ, without exception, may be invaded. This stage rarely appears in less than eighteen months after the appearance of the initial lesion, and may be delayed for even a score or more of years. There are but few organisms present, so it is evident that the accompanying necrosis is due to a state of allergy upon the part of the tissues. When the lesions are visceral there is apt to be intermittent fever, but this is by no means always the case.

Following the definite gummous manifestations there is usually a so-called latent period of varying lengths, during which time there are no evident lesions, but during which time either the nervous, arterial or some other structures may slowly become involved. This period may be interrupted at any time by the formation of gummata. This late apparently quiescent period may be short or it may continue indefinitely, sometimes for thirty or even more years, without there being evident any clinical manifestations. It should always be remembered that syphilitic changes in concealed organs only too frequently develop during this time.

The quaternary, or parasyphilitic, processes, namely, paresis and tabes, are true syphilitic processes as has been abundantly proved.[11] Tabes usually develops in from eight to twenty years after infection, but may arise either sooner or later. It is now believed that the occurrence of these late nervous manifestations

may be due to an infection with a special strain of organism that has an affinity for the nervous structures. It is difficult to say just what proportion of those affected with syphilis develop these nervous manifestations. According to White's figures, probably about 1 per cent become tabetic, but his figures may be low, inasmuch as not all of his early cases could be traced.

Special Types of Syphilis

Syphilis does not always run the course that has just been described; there are many variations. The chancre may be absent; in other instances there may be a chancre but no evident secondaries of any kind. In many instances of late lesions it is impossible to obtain a history of either an initial sclerosis or of any secondaries, and that in patients who are obviously trying to help the physician. In other words the disease may abort itself at an early period, or there may be no evident early lesions of any kind. It should always be remembered that a secondary roseola may be so faint as to escape notice. Some individuals have a marked secondary eruption and no further manifestations, although these cases are not nearly so numerous as we formerly believed. In some instances we find that ulcerative lesions predominate from the start, the so-called malignant cases, and severe lesions of the arteries, viscera, or nervous tracts may develop within a few months or even weeks after infection.

Malignant syphilis deserves special consideration. In this type the ulcerative processes begin at a very early date, due to allergy on the part of host. The disease usually starts in the characteristic way, but the papules ulcerate deeply and rupial crusts cover the ulcers, which are often very numerous, but fortunately confined to the skin or superficial mucous surfaces. There is usually cachexia and emaciation, and death from asthenia may supervene. In some instances even the chancre may assume an ulcerating aspect, but this is not usual. In other instances an apparently benign case may later assume a most malignant form. The ultimate fate of these patients should be watched with interest: Hutchinson believes that they eventually recover. As a rule such patients tolerate mercury badly; large doses cause further loss of weight without materially affecting

the disease. Small doses of arsphenamine, that is, about half of the usual doses, seem to work very well in some instances. In other cases a long course of tonic treatment may be necessary before any impression can be made upon the specific trouble. Arsphenamine should always be tried, both as a first and as a last resort.

Syphilitic fever has been described by many authors, but I shall follow Osler's[12] admirable account. He states that even in severe instances of infection the course may be afebrile throughout, and that even visceral syphilis does not necessarily cause fever. On the other hand a distinct elevation of temperature may occur even during the period of incubation. During the primary stage there is usually no change, but nevertheless fever has been reported. During the secondary stage from 20 to 25 per cent of all cases show some rise, and this may be intermittent, remittent, continuous, or irregular. The fever of the tertiary period is most interesting, for the fever may be severe and of long duration, and is most apt to simulate either typhoid or malaria, although occasionally it may be almost septic in character, and at times tuberculosis has been suspected. Both Manneberg[13] and Edwards[14] have called attention to the frequency with which syphilitic fever is associated with hepatic lues. Further references may be found in the writings of Birt,[15] Carrière,[16] Futcher,[17] Hermann,[18] Janeway,[19] Monier,[20] Newmann,[21] Scherck,[22] Phillips,[23] Musser,[24] Prentiss[25] and Morgan.[26]

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CHAPTER V

THE PRIMARY STAGE

The primary stage of syphilis clinically consists of the chancre and the enlargement of the satellite glands. Pathologically it consists of the development of the treponemata at the point of inoculation and their spread not only into the neighboring lymph nodes but into certain of the other lymphatic structures of the body.

The Genital Chancre

The incubation period has already been discussed; it is usually about four weeks, but may vary between three and seven weeks. According to Taylor[1] there are six ways in which genital chancres may manifest themselves, the chancrous erosion; the silvery spot; the dry papule or patch; the umbilicated papule; the purple necrotic nodule; the ecthymatous chancre. In addition the chancre is apt to undergo certain further transformations into: the elevated ulcer; the multiple herpetiform chancre; the parchment chancre; the annular chancre; the indurated nodule or mass; chancre with cream green membrane; infecting balanoposthitis.

The chancrous erosion is much the commonest early form and is really the primary lesion from which all chancres develop. It begins as a round excoriation, neither elevated nor depressed, and is of a dull red color. This form of chancre is most common upon the internal surface of the prepuce, possibly because it is protected from the air. It slowly increases in size and the edge and base become distinctly indurated. The base never sinks much below the level of the surrounding skin, and may be slightly elevated. When fully developed it has a smooth surface from which some serum oozes; there are no granulations. These lesions are usually solitary but may be multiple. Rarely a number of these chancres are grouped closely together and if of very small size may be mistaken for herpes, hence they are called multiple herpetiform chancres. They differ from herpes in that they do not itch or burn and that they have a darker color. When the lesion is superficial and the induration spreads

cut in a disk-like mass the lesion is called the parchment-like chancre. When the subcutaneous tissue is considerably involved and there is edema and induration the lesion is called the indurated nodule. Such lesions are apt to be found on the sulcus. When the growth is elevated above the level of the skin, it is known as the elevated ulcer. In many instances chancres are covered with a false membrane, incorrectly called diphtheritic, which may persist for weeks. This membrane is a combination of green and cream in color, and may later become black. In exceptional instances chancres may become necrotic.

Fig. 5.—This illustration portrays a fairly typical chancre of the skin of the penis. (Collection of Drs. Fordyce and MacKee.)

Fig. 6.—A chancre upon the glans resembles initial lesions of the skin. (Collection of Drs. Fordyce and MacKee.)

The silvery spot was first described by Taylor and is very rare. It usually occurs on the glands or the lips of the meatus, and "at first looks as if a pinhead-sized spot had been touched with carbolic acid or nitrate of silver." Induration slowly develops and an erosion later appears.

The dry papule is usually found upon the glands or the prepuce where this is not in contact with another surface, but may also occur upon the body of the penis or upon the skin or mucous membranes of the body. This type of initial sclerosis is usually but little indurated, involves the superficial tissues, is dry and gives out no secretion.

The umbilicated papule or follicular chancre begins as a pink-

ish elevation about the size of a milium with a minute depression in the center and resembles a lesion of molluscum contagiosum or an infected sebaceous gland. Later it becomes much more typical.

The purple necrotic nodule is rare. It occurs upon the glans or in the coronary sulcus, beginning as a small red spot which

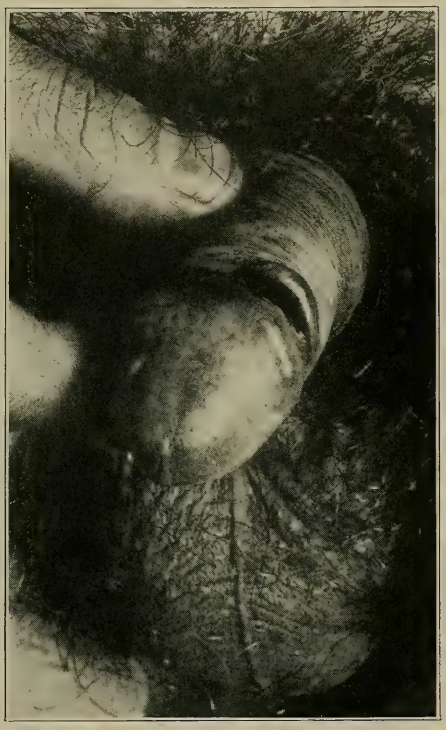

Fig. 7.—Chancres of the coronal sulcus with an indurated edge are absolutely typical; there is no other lesion that resembles them. (Collection of Drs. Fordyce and MacKee.)

gradually becomes purplish in color. This form of chancre is prone to necrotic degeneration, inasmuch as it is due to an obstructed blood supply.

The ecthymatous chancre is simply one that is covered by a pus crust, and may develop from any type, although it is usually found upon the body of the penis.

An annular chancre is one in which a ring-like induration develops, the center being comparatively free. It may occur upon the internal surface of the prepuce or upon the body of the penis.

Infecting balanitis begins as an erosion in the mucous layer of the prepuce and spreads peripherally until the whole prepuce is involved in a hyperplastic process. The prepuce is thickened, usually of a dull red color, and has a velvety excoriated appearance.

Chancres in the Male.—In the male the chancre is usually located in the coronary sulcus, especially near the frenum, but may occur upon the glans, the prepuce, the body of the penis, or even in the urethra. In the latter case a diagnosis of gonorrhea is apt to be made and the true condition overlooked, especially as a Neisser infection so frequently accompanies such chancres. As a rule there is but little induration, this can not be detected from the outside, and there is little disturbance to the flow of

Fig. 8.—Chancres may be accompanied by considerable edema. (Collection of Drs. Fordyce and MacKee.)

urine. In these cases endoscopic examination is always necessary in order to make an early diagnosis.

Chancres in the Female.—In the female Fournier reports the following distribution of chancres:

	Cases
Greater lips,	114
Lesser lips,	55
Fourchette,	38
Cervix,	13
Introitus vaginæ,	9
Urinary meatus,	17
Superior vulvar commissure,	2
Vagina,	1

Occasionally chancre of the greater lips is complicated by a marked edema of the entire labia. Chancres of the cervix are usually discovered accidentally, inasmuch as they usually give rise to no symptoms. It is also possible that the body of the uterus may be the site of chancres, although such cases are very difficult to demonstrate.

Special Types of Chancres.—One point in connection with genital chancres that can not be too strongly emphasized is the fact that many of the lesions are so insignificant and transitory that they attract but little attention on the part of the patient. The more cases of late syphilis that one sees the more impressed must he become with the fact that even the most intelligent patients who are obviously trying to help the physician can not recall any initial lesion, or at the most can remember but a tiny scratch that lasted only a few days. Then, too, we have all seen organisms found in the most insignificant looking lesions. In certain instances patients who deny any venereal infection are lying, in other instances they have suffered from an extragenital infection which was not recognized, but a large class does remain in which there was no typical chancre.

It is generally taught that chancres are solitary, but this is by no means always true as every syphilographer well knows. Gottheil[2] has recorded a number of cases where there was more than one lesion, in one case as high as thirteen, and even more have been reported by other observers. These chancres are usually all genital in situation, but a combination of genital and extragenital chancres may occur in the same individual. As Fordyce[3] points out multiple chancres may result from multiple simultaneous inoculation, from autoinoculation or from a slightly later and separate infection.

Complications.—Genital chancres are subject to certain complications.[4] A chancre may become infected with ordinary pyogenic organisms, and there will then be the ordinary signs of an acute infection, namely, heat, pain, redness, swelling and the discharge of pus. In addition the inguinal glands may suppurate. In the dispensaries a very interesting group of cases is seen not infrequently, and I have had the opportunity to follow a number of them in Dr. H. A. Fowler's service at the Freedmen's Hospital. The chancre begins in a normal way, but speed-

ily ulcerates and may involve a large portion of the penis. The tissue is distinctly granulomatous in appearance. The inguinal lymphatic glands frequently suppurate, so it is probable that a secondary infection is responsible for this change.

The organisms causing chancroid and syphilis may be inoculated simultaneously. In this case the former first appears, and may even have healed before the chancre becomes manifest. However, it is more common for the chancroid to persist and for it to gradually become enveloped in a hard indurated ring. If a chancroidal infection be grafted upon a developed chancre the resulting lesion is almost typical of chancroid except that there remains a deep induration. If the treponema be inoculated into a chancroid the result is a slowly developing induration.

Associated with the chancre it is not uncommon to find a crop of venereal warts, which are simply due to the irritation. At times the initial sclerosis may lose its induration as other secondary symptoms develop, become covered with a false gray membrane and present all of the characteristics of either a mucous patch or a condyloma.

Phagedenic ulceration was formerly common if one can believe the accounts of the older writers. It was supposed to occur more frequently in those of depraved bodily conditions. The ulceration would travel up the penis either rapidly or slowly and could only be checked by the most vigorous cauterization. At the present time there is a rather general feeling that such a complication is due to a secondary infection.

In addition to the chancre itself, the neighboring inguinal glands become enlarged, hard and shotty, while remaining discrete. This usually takes place in from two to three weeks after the appearance of the first sign of the chancre. The glands never break down unless secondarily infected. At times the dorsal lymphatic trunk of the penis may be involved so that it resembles a cord. This may or may not be red in color. A hard nodule may develop in this cord at the upper portion of the penis near the root.

Diagnosis of Genital Chancres.—The chancre in the male must be distinguished from chancroid, herpes progenitalis, cancer and scabies. In chancroid the incubation period is but a few days,

while in chancre it is from three to five weeks. The chancre is more apt to be solitary than in the case of chancroids. The typical chancre has a distinct rim of induration that lacks in the chancroid. In the chancre the satellite glands are hard, discrete and shotty, while in chancroid they are soft, and tend to suppurate. However, it has always been recognized by experienced men that it is frequently impossible to make the diagnosis from physical examination alone, hence it was the practice in many clinics to wait until the secondaries appeared before beginning treatment. At the present time the lesion should always be dark-fielded for treponemata, remembering that one search may not reveal them, especially if the lesion has been treated with antiseptics. The Wassermann results in the initial stage of syphilis as given by Craig[5] are as follows:

Week after appearance of chancre	*Total number examined*	*Total positive reactions*	*Per cent positive*
First	65	18	27.6
Second	122	62	50.8
Third	123	79	64.2
Fourth	134	98	73.1
Fifth	39	31	79.4

Hence it is evident that a negative Wassermann reaction by no means excludes syphilis. On the other hand a patient with a positive reaction may have some other type of genital lesion, so a positive complement-fixation test by no means makes it certain that the lesion under consideration is syphilitic. The luetin reaction is of no value in the primary stage. Excision of the lesion and its examination by a competent pathologist should almost invariably reveal the true nature if syphilitic, for, as will shortly be pointed out, the microscopic picture of even an early chancre is pathognomonic.

The lesions of herpes progenitalis begin as superficial vesicles upon an inflamed base: they itch and burn, and there is usually the history of repeated attacks. The neighboring glands do not become enlarged. Hence there is only one type of chancre that might be confused, namely, the multiple herpetiform one, and this may usually be distinguished by the lack of sensory disturbance and the rapid enlargement of the lymph nodes, as well as by the finding of the causal organisms.

Cancer develops in the old, is of slow development, and does not cause enlargement of the glands nearly so rapidly as does chancre. No treponemata can be demonstrated. Under no circumstances should a bit of tissue be removed for microscopic examination if malignancy be suspected, unless this be done with the actual cautery, for it is generally held to be unsafe to cut into a cancer and not cauterize at the same time, lest the development of metastases be favored.[6]

Scabies causes trouble much more frequently than the text books would have us believe; the combination of genital sores and an eruption has caused many a case to be diagnosed as syphilitic when a little sulphur ointment would have effected a cure. In reality the proper differentiation is usually easy, for in scabies the lesions itch intensely especially at night, and the finding of lesions between the fingers, upon the flexor surfaces of the wrists, in the bends of the elbows and axillæ, as well as upon the lower abdomen, the buttocks, and inner surfaces of the thighs is characteristic. The genital sores are usually upon the body of the penis rather than upon the glans, usually show scratch marks and are not indurated. There is no involvement of the glands.

In women the diagnosis must be made along the same general lines, but usually it is not necessary to exclude scabies, inasmuch as the lesions of this disease but rarely affect the female external genitals.

Extragenital Chancres.—From 5 to 6 per cent of all chancres are located upon portions of the body other than the genitalia. As already indicated by no means all of these lesions are innocently acquired. In Fournier's series of 1124 cases there was the following distribution:

	Cases
Lips,	567
Tongue,	75
Tonsil,	69
Gums,	11
Soft palate,	4
Inner surface of cheeks,	1
Chin,	54
Cheeks,	24
Eyelid,	21

Nose,	18
Forehead,	2
Scalp,	3
Upper limb,	78
Anus,	77
Breast,	59
Trunk,	33
Lower limbs,	14
Neck,	14

In Bulkley's[8] cases the location of the lesions was as follows:

	Cases
Lips,	1,810
Breasts,	1,148
Buccal cavity,	734
Hands,	462
Eyelids,	372
Tonsils,	307
Deep throat,	264
Tongue,	157
Chin,	146
Cheek,	145
Trunk,	100
Nose,	95
Anus,	87
Perigenital region,	77
Legs,	73
Forearm,	59
Neck,	47
Gums,	42
Forehead,	37
Ears,	27
By vaccination,	1,863
Blood letting,	745
Circumcision,	179
Tattooing,	82

Montgomery's[9] 58 cases were distributed as follows:

	Cases
Lips,	25
Tongue,	3
Gums,	1
Corner mouth,	1
Tonsil,	1
Cheek,	1

Eye,	1
Neck,	1
Abdomen,	5
Breast,	1
Nates,	1
Arm,	3
Fingers,	7
Wrist,	1
Forearm,	2
Back of hand,	1

In Cole's[10] 61 cases there was the following distribution:

	Cases
Lips,	43
Tongue,	1
Tonsils,	3
Neck,	1
Jaw,	1
Breast,	1
Abdomen,	1
Hands,	10

In my[11] series of cases, the lesions were distributed as follows:

	Cases
Upper lip,	5
Lower lip,	5
Cheek,	2
Chin,	1
Nose,	1
Tonsil,	4
Anus,	3
Finger,	3
Palm,	1
Foot,	1
Arm (vaccination)	1
No chancre,	1

Chancre of the Lip.—It can plainly be seen that extragenital chancres are more common upon the lips than in any other situation. The two sexes are about equally affected. Chancre of the lip is very rare in negroes: I have seen but one instance. The lower lip is stated to be more frequently attacked than is the upper. There is usually but one lesion, and this is commonly situated at the onset at the junction of the cutaneous and vermil-

ion surfaces, although both are shortly affected. It may assume any of the forms described under genital chancre, but usually there is a protruding mass that varies in size from one-half to one inch, and that is covered by a thick dark brown scab, which when removed is found to cover a mass of granulation tissue of a deep red color. There is a marked ring of induration around and beneath the lesion. The submental and submaxillary glands swell very rapidly, and often assume a considerable size. While the clinical diagnosis is usually rather easy, it can be confirmed

Fig. 9.—Chancres of the lip are usually somewhat larger than are genital lesions, but in other respects closely resemble them.

by finding treponemata in the lesions, preferably by means of the dark-field illuminator. Cancer of the lip must always be excluded, and, as a rule, this is not a difficult undertaking, for cancer rarely affects women, the young, or the upper lip. In addition in the case of cancer there is always the history of a precancerous lesion, and the growth of the cancer is slow, at least in the vast majority of instances. In cancer the lymph nodes do not enlarge so quickly as in syphilis, neither do they reach a large size in a few weeks. Blastomycosis of the lip might also cause some trouble in diagnosis, but here too the development is much

slower, and the yeast-like organisms can be found in pus expressed from one of the miliary abscesses. The vast majority of chancres of the lip unquestionably come from kissing some one with either an initial sclerosis or a mucous patch.

Tongue.—Chancres of the tongue are usually solitary, but there may be two or even more. Either the tip or the dorsal surface near the tip is the usual site. The lesion begins as a superficial excoriated area that soon becomes indurated, and that may then appear as an indurated ulcer, as a nodule or as a slightly fungous growth, with the characteristic red color, and

Fig. 10.—In labial chancres the rim may be raised and hard. (Collection of Dr. Richard L. Sutton.)

the marked induration of the edges and base. The submental and submaxillary lymph nodes soon enlarge. Cancer must be differentiated, and this can be done by the rules laid down under chancre of the lip. Lesions in this site may arise from kissing, from perverted sexual habits or from the use of infected eating utensils.

Tonsil.—Chancres of the tonsil have recently been carefully studied by Smith,[12] who finds that primary lesions in this location are certainly much commoner than has generally been believed, inasmuch as many of them escape recognition because of the atypical forms assumed. Wilson,[13] in a review of 6000 cases of

extragenital chancre found that 600 were tonsillar. The right tonsil is more affected than is the left, and women suffer more frequently than do men. It is claimed by some physicians, including as keen an observer as Osler, that these lesions usually result from improper practices, but Smith disagrees with this view, and believes that kissing is the most frequent cause, and that the careless use of eating and drinking utensils ranks next.

Fig. 11.—Chancres of the tongue are similar to those of other mucous membranes. (Collection of Drs. Fordyce and MacKee.)

He further states that pipes, mouthpieces of wind instruments, nursing bottle nipples, cigar stubs, tonsillotomes, eustachian catheters, mouth to mouth insufflation, and a common blowpipe in glass factories have all been reported as modes of conveying the infection.

The first symptom noted by the patient is usually sore throat, with some stinging pain. Glandular enlargement is prompt. The tonsil is always enlarged and of a deep red color, and the pillars are likewise red. The fact that both the tonsil and the neigh-

boring parts are not infrequently covered by a membrane often causes the condition to be mistaken for a Vincent's angina or diphtheria. Fournier describes five clinical varieties, erosive, ulcerative, quinsy-like, diphtheroid and gangrenous.

The condition must be differentiated from acute tonsillitis, peritonsillar abscess, Vincent's angina, diphtheria, tuberculous ulcer, malignant disease, mucous patches and gumma of the tonsil. The fact that the adjacent lymph nodes become enlarged in from two to three weeks and that there is but little pain are very important points in making a diagnosis. Any induration of a local lesion is also most important. Usually there is a lack of fever or of any ether evidences of acute infection. The findings of the dark-field illuminator must be interpreted with discretion, inasmuch as the mouth swarms with spirochetes.

Gums.—Chancres of the gums are rather unusual, and frequently are not promptly recognized as is proved by Davis's discussion of Smith's paper. These lesions usually result from a visit to a careless dentist, and sarcoma is very likely to be suspected.

Skin.—Lesions upon the glabrous skin are alike in most characteristics. They begin either as superficial excoriations or papules, that in the course of two or three weeks grow to a diameter of from three-quarters to one and one-half inches. The skin over the center soon ulcerates, showing a mass of red tissue, that closely resembles granulation tissue, although it is usually smoother upon the surface. This is surrounded by a firm raised collar of induration, which also is often evident at the base. In some instances the ulceration may extend to a considerable depth, but is usually comparatively superficial. The appearance, especially the color, is usually characteristic. The neighboring glands enlarge in from two to three weeks. It is in this class of cases that the dark-field illuminator is of especial value in establishing an early diagnosis. Of the lesions upon the skin those upon the fingers are commonest, being especially prevalent in physicians and nurses: at times they may result from fingering the genitalia, from bites, or much more rarely from infected intermediate sources.

These lesions must be told from tuberculous lesions, epitheliomata, blastomycosis and from ordinary superficial infections,

and the differential diagnosis can be made by the rules already laid down.

Anus.—Chancres of the anus in women frequently result from the backward flow of discharges from the vulva, and not from

Fig. 12.—Chancres of the glabrous skin are frequently large in size. (Collection of Dr. T. Caspar Gilchrist.)

Fig. 13.—Chancres of the fingers are not rarities in the medical profession. In this instance the infection was acquired in examining for adenoids with an ungloved finger.

pederasty. In men they are most apt to result from the latter practice. I have seen one case where two chancres of the anus were diagnosed by an anal surgeon as thrombosed piles. These lesions but rarely come from the use of infected toilets, although such a means of infection is theoretically possible.

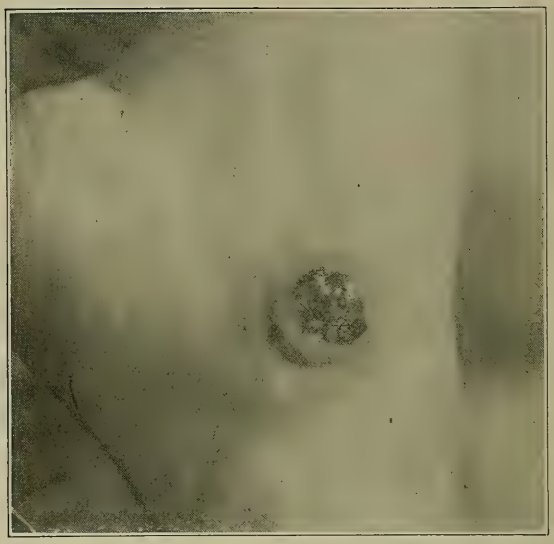

Fig. 14.—Chancres of the foot are very rare. This typical lesion was acquired in an unknown way during a stay in a hospital.

Fig. 15.—Anal chancres are by no means unknown; they frequently tend to have a verrucose surface. (Collection of Drs. Hall and Castle.)

There seems to be no good reason to suppose that the course of syphilis after an extragenital infection is any different than that following a genital infection, for the pathology is essentially the same. However, White[14] feels that inasmuch as these lesions

Fig. 16.—At the edge of a chancre the perivascular infiltration so characteristic of syphilis can always be seen. (Collection of Drs. Fordyce and MacKee.)

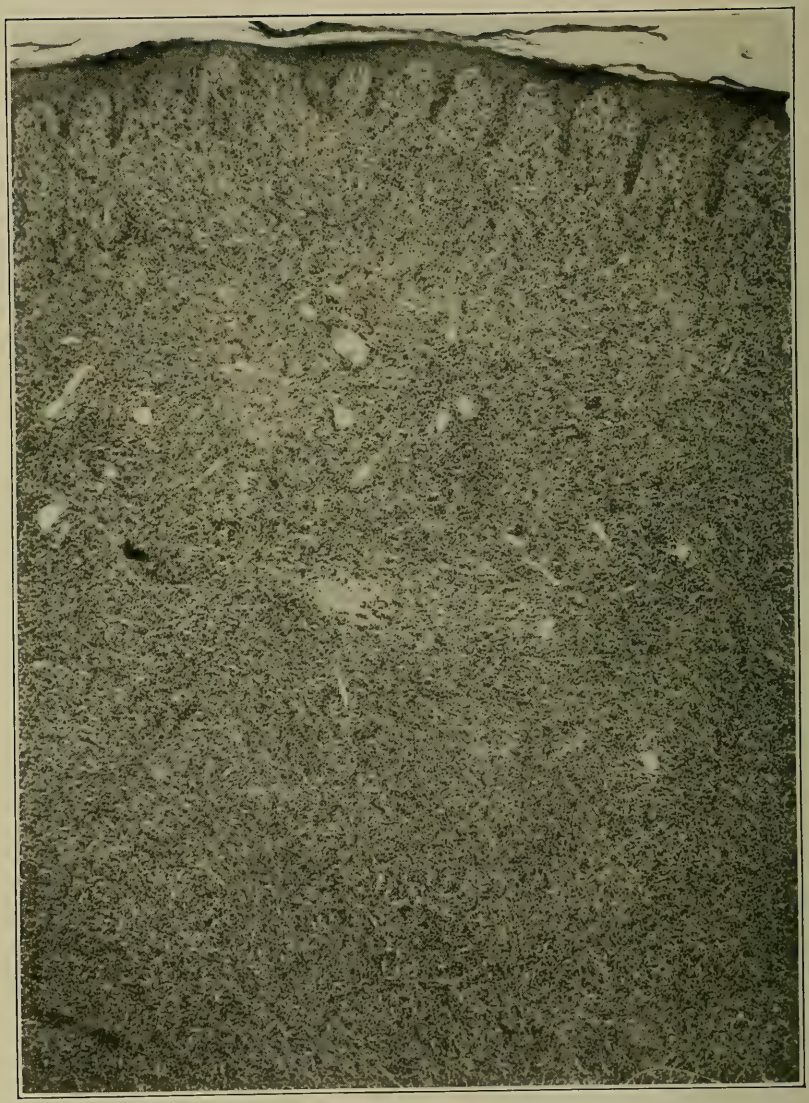

Fig. 17.—The interior of a chancre presents an almost uniform infiltration with round and plasma cells. (Collection of Drs. Fordyce and MacKee.)

are frequently the result of trauma, the organisms may be more deeply planted than usual, and that the result may be worse. It is, of course, true that extragenital chancres are usually larger than are the genital ones, but I can see no difference in the subsequent course of the disease.

Pathology of Chancre.—In the chancre the main changes are found in the cutis,[15] the earliest being the formation of new capillaries, and the grouping about them of lymphocytes and plasma cells. This infiltration is at first circumscribed, but later becomes diffuse, so as to fill the entire field. The endothelium of the capillaries is swollen and proliferated so as to narrow or even occlude the lumen, and even the larger vessels show an increased thickness. Giant cells are occasionally found. From the newly formed granulation tissue connective tissue is developed, this scleroses and leads to induration. The epidermis presents a varied picture, depending on whether or not there is pressure from the infiltration or retrograde changes with erosion and ulceration. As a result of the pathologic changes nutrition is apt to be interfered with and loss of substance not infrequently results.

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CHAPTER VI

EARLY CUTANEOUS LESIONS

The skin manifestations that occur within a few weeks after the appearance of the chancre are due to a widespread dissemination of the treponemata, and are simply one phase of a general septicemia. It is certain that some at least of the mucous membranes are likewise involved at the same time. It is well known that the eruption may be totally absent although other manifestations are present. In White's statistical study of over five hundred cases of secondary syphilis only about half showed cutaneous lesions. However, it is probable that about 80 per cent of all patients have some cutaneous manifestations early in the course of the disease. George Henry Fox[1] has recently suggested a new classification for these lesions, and this has been adopted by the American Dermatological Association: hence, with a few minor variations, it will be followed in this book.

- Macular
  - Roseolar.
  - Annular.
  - Vitiligoid.
- Maculopapular.
- Papular
  - Miliary—disseminate, corymbose, annular.
  - Lenticular—disseminate, corymbose, hypertrophic, confluent, squamous.
  - Discoid—disseminate, annular, confluent, squamous, moist.
- Papulopustular.
- Pustular
  - Acuminate.
  - Obtuse.
  - Ecthymoid—crustaceous, rupial, ulcerative.
- Vesicular.
- Neurosyphilide.

The early lesions have certain general characteristics.

Distribution.—They are usually symmetrical, and more or less generalized. In the vast majority of instances the trunk is affected, and the neck and limbs as well. In some types of lesions the face may be spared, although this is by no means a general

rule, except in the case of macular lesions. In many instances the palms and soles are involved. The mucous membranes of the mouth are often the site of lesions.

Size.—The lesions are usually comparatively small, the largest primary lesions never being over three-fourths of an inch in diameter and even this size being rather unusual. In the annular lesions of negroes a diameter of several inches may be reached.

Color.—The color is usually a cold pink, much less brilliant than that seen in most other cutaneous eruptions. After the lesions have persisted for some little time pigment may develop in them so that they will assume a brownish tint. Unfortunately the idea is ingrained in many physicians and students that a "raw ham color" is almost invariably present, but this is only exceptionally true, except in some of the lenticular papules. When the lesions begin to involute and become scaly, they have a whitish color, due to the scales.

Configuration.—There is no characteristic arrangement, except in the annular and corymbose syphilides. However, there is always a marked tendency for grouping of the lesions to occur.

Development.—The early lesions develop rapidly, usually in the course of two or three days, although it frequently takes several weeks before the maximum development is reached. In the case of the annular lesions in the negro a month or more is necessary for the lesion to attain its greatest size. If left untreated the syphilides usually disappear spontaneously in the course of several months, although this is not always the case. The lesions may entirely disappear, they may leave some traces of pigment, or rarely even scar formation or even keloids may result.

Polymorphism.—Several varieties of lesions are usually present, although one type always predominates. A few papules and pustules are very apt to occur in association with any type of lesion.

Subjective Symptoms.—There is no pain or burning associated with the secondary syphilides and it is rare for them to even itch, especially in the white race, although in the negro at least 5 per cent of them are accompanied by more or less intense itching. In condylomata, especially those around the anus, the itch-

ing may be severe, and these lesions are usually tender and often painful. Lesions of the mouth are not infrequently tender.

Macular Syphilides

The macular syphilide occurs in over 50 per cent of all cases in whites where an eruption is present, but only in about 15

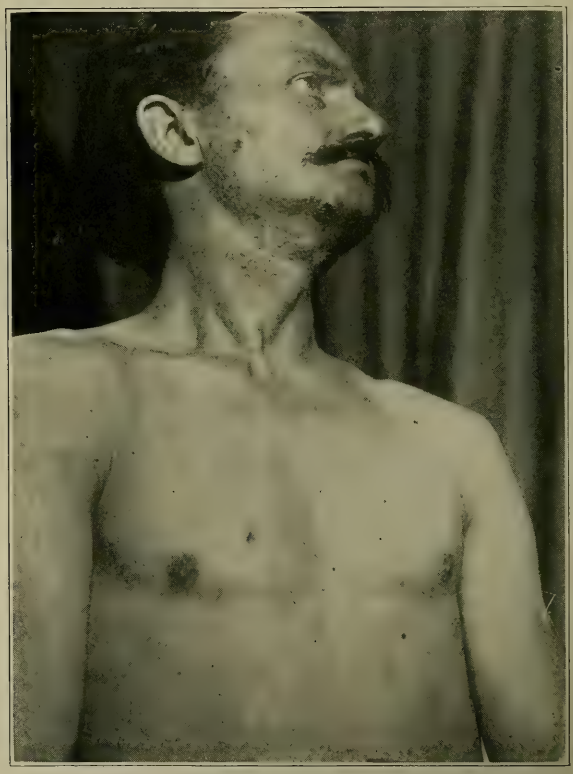

Fig. 18.—Macular syphilides are pale and difficult to photograph. This patient also has a chancre of the chin. (Gilchrist's case.)

per cent of the blacks. Hence in the former it is the predominating type of eruption, while in the latter it is rather unusual. As a rule it predominates upon the body and limbs and spares the face, and is decidedly unusual upon the palms or soles. Local irritation may increase the number of lesions upon some particular portion of the body. The lesions vary considerably

Fig. 19.—The large macular syphilide tends to become pigmented as it ages.

in size, although not to any great extent in the same individual, being from one-fourth to three-fourths of an inch in diameter, and roughly oval in shape. They are flat, so can not be felt by the palpating finger. At first their color is a pale pink, so pale in some instances that they may be easily overlooked unless one searches for them in a good light. Ormsby[2] suggests that they should be looked for with a lens that is tinged with cobalt blue, but an even better plan is to use a Cooper-Hewitt lamp. As the lesions become older they become browner in color, and this is more characteristic of the larger than of the smaller ones. Their rarity in the negro is rather difficult to explain: at first blush it might seem that they would not be visible upon a dark skin, but as a matter of fact they are just as rare in the mulatto as in the pure black.[3]

The pathology of these lesions has been studied by Unna,[4] Fordyce,[5] Dennie[6] and others, and there is substantial agreement as to both fundamentals and details. There are comparatively few changes, chiefly an erythema with dilatation of the vessels in the upper portion of the corium, and a moderate amount of perivascular infiltrate with lymphocytes and plasma cells. The vessels may show some endothelial changes. It is agreed that the changes begin primarily in the perivascular lymph spaces.

These macular lesions must be told from pityriasis rosea, erythema multiforme, drug rashes, tinea circinata, tinea versicolor, measles, German measles, typhus, the early stages of scarlet fever and seborrheic dermatitis.

Pityriasis rosea is very frequently mistaken for syphilis, inasmuch as neither the genitourinary men nor the general practitioner seem able to recognize this disease, which is a not uncommon one. It is an undoubted fact, as has been noted by Strobel, that pityriasis rosea is more apt to occur in the syphilitic than in the nonsyphilitic, but yet in several definitely nonsyphilitic cases a suggestive Wassermann reaction has been observed. However, the clinical diagnosis is not difficult for a dermatologist, for not only is pityriasis rosea unaccompanied by any other signs of syphilis, although it is true that a pharyngitis or even a tonsillitis may be present. The lesions in the individual always vary markedly in size, are oval and the long axis of the

lesions is parallel with the direction of the ribs. The lesions almost invariably tend to clear up in the center, and then the center has a yellowish tinge, while the borders are of a bright rosy color. The lesions are covered with fine furfuraceous scales even at an early date, which is certainly not true of syphilis. There are no treponemata in the lesions.

In seborrheic dermatitis the lesions are scaly and of a bright color, and some large ones are almost invariably present. There is usually the history of the lesions first appearing in either the

Fig. 20.—Pityriasis rosea is more frequently mistaken for syphilis than it is correctly diagnosed.

axillæ and groins, or upon the midline of the chest and back. There is marked tendency for an early formation of scales and also for some of the lesions to be annular, while there is always a considerable variation in size. Some degree of itching is almost invariably present. There are no constitutional symptoms and no other signs of syphilis.

Erythema multiforme is usually more profuse upon the backs of the hands and forearms than elsewhere, and it is far from rare to find it entirely confined to these locations. When the trunk is

affected the lesions are apt to be extremely large. There is always a marked tendency for the lesions to become annular, and a central vesicle is not uncommon. It is very important to note that they are never scaly. Then, too, there is usually the history of recurring attacks, often at definite intervals. The lesions do not itch, but are apt to be somewhat tender. The mu-

Fig. 21.—Acute seborrheic dermatitis may resemble syphilis.

cous membranes may show inflammation and even superficial ulceration, but never true mucous patches. The general symptoms that sometimes accompany this disease may at times be slightly suggestive of syphilis, but there are no other definite findings of syphilis, either laboratory or physical.

Drug rashes are almost invariably of a much brighter color than are luetic eruptions, and some itching is almost constant. There is usually the history of the ingestion of some drug, and the stopping of it causes the disappearance of the rash. Again it is important to note that both copaiba and cubebs are especially apt to cause cutaneous erythemata, and many a person who has taken one of these drugs for gonorrhea has been diagnosed as a syphilitic because of the resultant eruption.

In tinea circinata the lesions are usually comparatively few in number, asymmetrically distributed, scaly from the onset, and do not appear at once, but in successive crops. The edge is very inflammatory and usually shows minute vesicles. The microscope will show the presence of spores and mycelium. There are no other signs of syphilis.

Tinea versicolor is mentioned in all of the text books as frequently being mistaken for syphilis, but I have never seen any student confused on this point. The lesions are very chronic, distinctly fawn colored, not inflammatory, and usually confined to the chest and back. The lesions vary much in size. There is a considerable amount of furfuraceous scaling, and the parasite can easily be demonstrated under the microscope, it only being necessary to scrape off a few scales, add a drop of a 15 per cent solution of caustic potash, add a cover slip and then examine under the high power.

The lesions of measles come on abruptly with fever, coryza and Koplik's spots. They are more inflammatory than are those of syphilis, and are usually much more blotchy in appearance. They are, of course, commoner in children than in adults. Some degree of glandular enlargement is not at all uncommon.

The eruption of German measles is apt to be very transient, and while their light color, and also the presence of marked cervical adenitis may at first cause the physician to think of syphilis, the fact that this disease occurs in epidemics and the lack of any other signs of syphilis should always enable the physician to make a correct diagnosis, even if none of the laboratory aids are employed.

Scarlet fever usually shows a characteristic tongue and throat, and the onset is stormy. The eruption speedily becomes more diffuse than that of syphilis, and much more brilliantly colored.

Typhus fever is accompanied by a stormy onset, high fever, delirium, and enlarged spleen, although too much stress should not be put upon this latter point, as Wile[7] has shown that the spleen in secondary syphilis is frequently enlarged. The general clinical picture and laboratory findings are both markedly different.

There are two distinct types of annular macular lesions,[8] first where some few or occasionally many of the ordinary roseolar lesions clear in the center and spread peripherally, and secondly the neurosyphilides of Unna. They are both rare. The first named occasionally develops upon the faces or even the bodies of the freshly infected, and is simply a modification of the usual type of eruption. The latter is stated to be a totally distinct affection. These lesions must be told from pityriasis rosea as MacKee[9] has pointed out. In case the general signs and laboratory findings leave one in doubt, the question can always be settled by doing a biopsy, and examining the cut and stained specimen, as the changes in syphilis are characteristic.

The vitiligoid macular syphiloderm is also called pigmentary syphiloderm, leucoderma syphiliticum, and vitiligo acquisita syphilitica. It is distinctly uncommon and usually affects the necks of women. It was first described by Hardy[10] in 1853, and subsequently by Fournier, George Henry Fox,[11] Atkinson,[12] Taylor,[13] and others. Sutton[14] has recently described the histopathologic picture. Much confusion has arisen concerning this, some men considering it a hyperpigmentation and some a depigmentation, but Taylor's observations should serve to clear up the question. He states: (1) Syphilis may produce pigmented macules without change in the intervening skin; (2) hyperpigmentation with vitiligo; (3) destruction of pigment so as to simulate vitiligo. This variety of syphilide usually develops in from six to twelve months after the appearance of the initial sclerosis, but may not appear until several years later. There are always whitish lesions which are roughly oval in shape and which vary in diameter from one third to three-quarters of an inch, and which are fairly well defined. Surrounding them is a diffuse hyperpigmentation, which in the dark skinned may be very difficult to detect. By some it has been stated that the whitish spots are simply the remains of old syphilitic lesions, but this is cer-

Fig. 22.—Syphilitic leucoderma usually affects the necks of women. (Collection of Dr. Richard L. Sutton.)

Fig. 23.—The depigmented areas in syphilis may be very small. (Collection of Dr. Richard L. Sutton.)

tainly by no means always true. In still other instances areas of increased pigmentation first appear in the form of macules about three-fourths of an inch in diameter, the color being that of chloasma, and resembling patches of dirty skin. The intervening skin is distinctly lighter than normal. The dark patches may coalesce. The condition must be diagnosed from both leukoderma and chloasma, from tinea versicolor and leprosy. The last-named can be excluded by the fact that no anesthesia is present, and tinea versicolor by the fact that the syphilitic lesion is never scaly. The peculiar configuration will usually serve to exclude either leucoderma or chloasma, or if not, the laboratory findings will make the diagnosis certain.

Under the heading of macular syphilis must also be mentioned the variety described by Ehrmann.[15] Here there are patches which are slightly elevated, present a branching arrangement, with many twigs joining a common trunk, or else a diffuse network. The color is a livid red. As Ehrmann has noted an obliterating endarteritis and found the treponema in the vessel walls, it is more than probable that he is correct when he assumes that the distribution of the lesions is determined by the vascular distribution..

Trimble[16] has called attention to a reddish, erythematous mottling of the chin as association with secondary syphilis. The point of the chin is usually spared, and at times the lesion may creep up around the commissures of the mouth so that a portion of the upper lip may be involved. The lesion is commoner in women than in men, probably due to the beard of the male hiding the characteristic slight color changes.

Maculopapular Syphilide

The ordinary lesions of maculopapular syphilis are simply a cross between macules and papules. They occur chiefly on the trunk and limbs, and the face is usually spared, also the palms and soles are but rarely affected. In general appearance the lesions unquestionably resemble the wheals of urticaria, but are persistent and not transient. They are oval in shape, the long axis tending to be parallel with the direction of the ribs. In length they vary from one-third to two-thirds of an inch. In

color they are pale pink, and the definition is sharp, and they are distinctly palpable. In the negro these lesions occasionally become annular. The lesions run about the same course that the macular lesions do. The differential diagnosis must be made from urticaria and a drug rash. In urticaria the lesions are rarely so profuse, they are transitory and usually itch intensely,

Fig. 24.—A maculopapular syphilide may closely resemble urticaria.

and a wheal can be produced by rubbing the skin. However it should be noted that a mild factitious urticaria is not infrequently present during the secondary stage of syphilis. Drug rashes are of short duration, follow the ingestion of some drug, are brilliantly colored and usually itch. They speedily disappear when the use of the drug is discontinued. Pathologically there

Fig. 25.—In maculopapular syphilides there is a characteristic perivascular infiltration.

is considerably more of perivascular infiltrate than in the macular form, but not so much as in the papular syphilide.

Miliary Papular Syphilide

Other names for this eruption are syphilitic lichen and small acuminate syphilide. The miliary or follicular lesions are much more common in the negro than in the white. In one hundred and seventy-six cases of secondary syphilis in the negro ten of this variety were noted. In whites it is unusual. The lesions usually develop symmetrically over the whole body, with the exception of the palms and soles which are but rarely affected. The face usually shows lesions. The lesions appear around the hair follicles as firm pointed or rounded papules that are from one to three millimeters in diameter and usually about one millimeter in height. At the apex there is frequently a scale or even a minute pustule or vesicle. In the white race the lesions are of a salmon color, but in the negro the color is that of the normal skin. As the lesions become older there is frequently the deposit of some pigment. Involution occurs through the absorption of the inflammatory exudate and is accompanied by some scaling.

There are a number of special types of the eruption. Usually the lesions are widely disseminated over the entire body, with a marked tendency towards grouping, but occasionally this tendency is so great that the lesions become corymbose, with a central bull's eye, around which are clustered very numerous

Fig. 26.—Miliary or follicular syphilides are more common in negroes than in whites. This patient also had broken-down syphilitic glands of the neck.

closely packed lesions. There may be two distinct types of annular lesions as I have pointed out, one where a single papule clears up in the center and spreads peripherally so as to form a ring, and the second where a number of papules unite to form a ring, either hollow or solid. The lesions produced from a soli-

tary papule are usually rather small, rarely reaching a diameter of more than three-fourths of an inch, and rings within rings are but seldom seen. The borders are slightly elevated and may form either complete circles, or segments of circles. Several rings may coalesce so as to form irregularly shaped figures. The

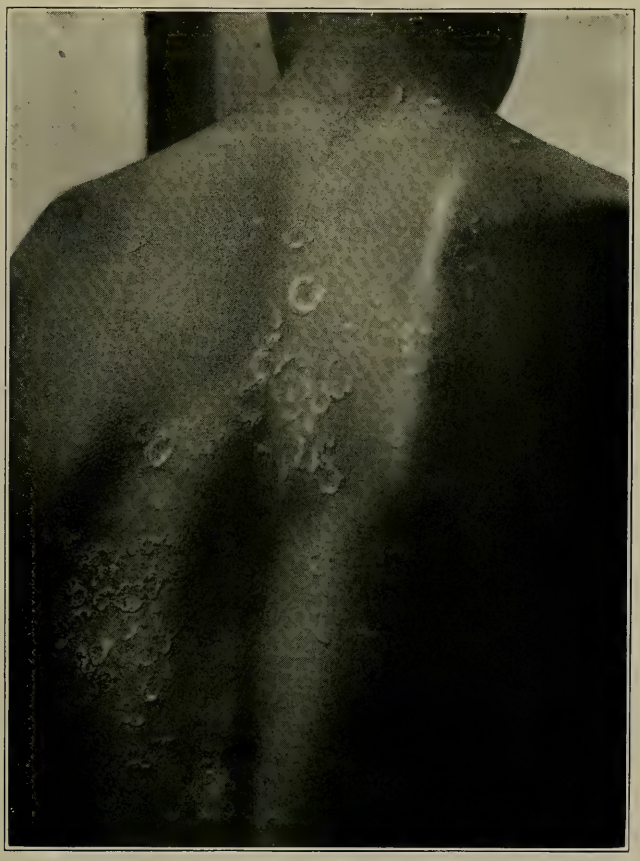

Fig. 27.—A miliary syphilide may become annular.

edges are covered with fine, closely adherent scales of a grayish color. The center may be more or less deeply pigmented, normal in color or may even show a lack of pigment. The lesions are more common around the angles of the mouth and eyes than elsewhere. When a number of lesions unite to form a ring we find

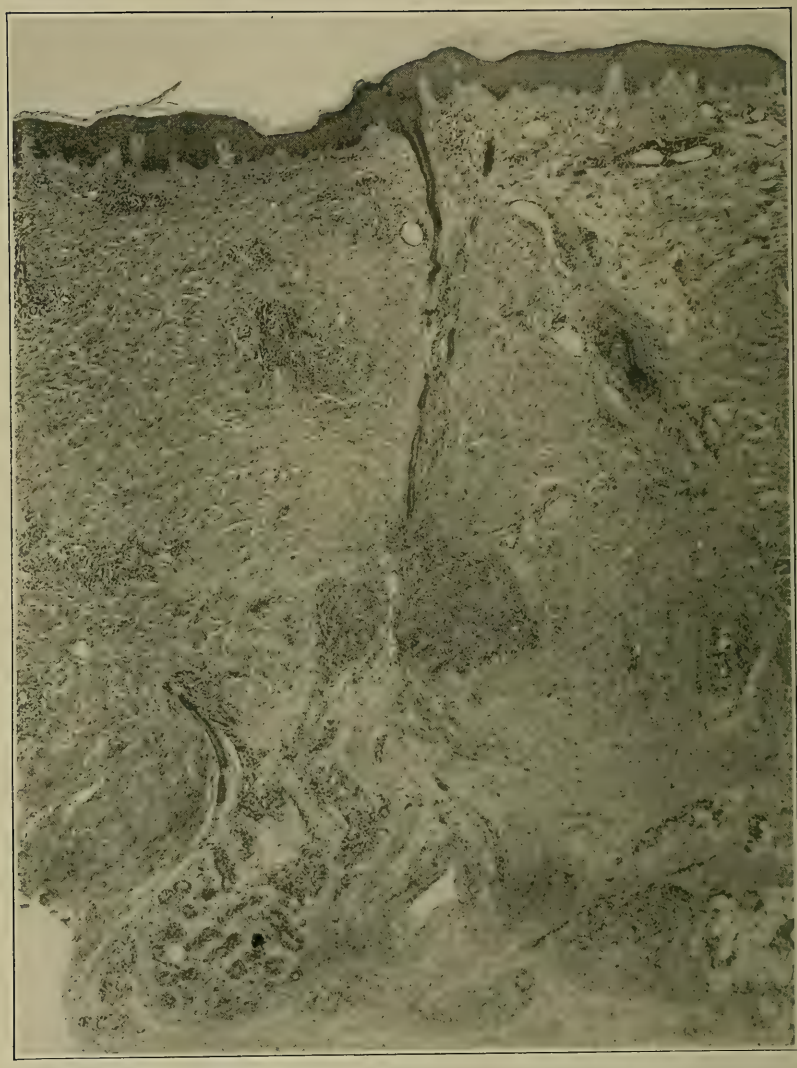

Fig. 28.—In a miliary syphilide the infiltration is usually around a hair follicle: in this instance it is especially marked around a sweat duct. Note the perivascular infiltration in other portions of the corium. (Collection of Drs. Fordyce and MacKee.)

that this may be done in either one of two ways. Either a solid ring is first formed, the central papules of which first undergo involution, or a number of papules may group themselves so as to form a hollow ring. Occasionally the number of papules is so great that practically every follicle of the body is affected, and then the disease markedly resembles pityriasis rubra pilaris.

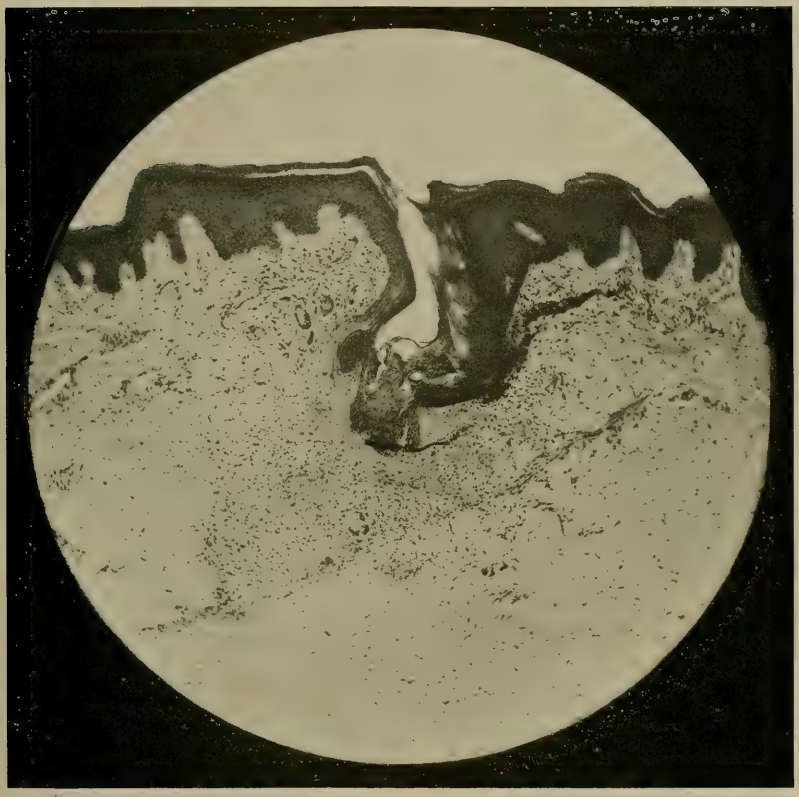

Fig. 29.—The characteristic perifollicular infiltration of a miliary syphilide can be well seen in this illustration. Giant cells are rather unusual in early syphilis. (Collection of Drs. Fordyce and MacKee.)

Pathologically the changes are in the neighborhood of the hair follicles, hence extend deep down into the tissues. There is a marked perivascular infiltrate with small round and plasma cells.

The miliary syphiloderm must be distinguished from pityriasis rubra pilaris, keratosis pilaris, psoriasis and small papular ec-

zema. The lesions of the first named develop much more slowly and are not so inflammatory as in the case of the specific lesions. Usually there occur black-capped papules upon the dorsal surfaces of the proximal phalanges of the fingers, a plantar and palmar hyperkeratosis, a facial seborrhea and a pityriasis of the scalp. Other signs of syphilis are lacking, and the histologic findings in the two diseases are essentially different. Keratosis pilaris is also essentially chronic, is associated with a very dry skin, and begins in childhood. The lesions predominate upon the extensor surfaces of the limbs and are not inflammatory. They frequently contain horny plugs. Some at least of the lesions of psoriasis are larger, and all are much more profusely covered with fine white powdery scales, that show minute bleeding points when removed. The lesions of eczema are usually much less widely disseminated, tend to itch, and usually become confluent. It should always be remembered that eczema and syphilis may coexist.

Lenticular Papular Syphilide

By a lenticular papular syphiloderm is meant one in which the papule is fully developed, being either acuminate, semiglobular, or more commonly flattened out, but always protruding well above the surface of the skin. The disseminate form involves the trunk, limbs, face, and frequently the palms and soles. As a rule the lesions are more profuse upon the back than upon the chest or abdomen, and are more numerous upon the flexor rather than the extensor surfaces of the limbs. These lesions vary in diameter from one-eighth to one-half inch, are round in shape and well defined. They are firm to the touch. Their tops may be flat or may be semiglobular in shape. At first they are smooth and glossy, but there may be many scales from the onset, and as they involute they almost invariably become scaly. The color varies from a pink to deep salmon red. Below the knees the color may be purplish, and in those having circulatory disturbances this same hue may be present. Upon the face they are very prone to develop just below the hair line, even in the bald they are not infrequently found in this location. Like other syphilides they show a marked tendency towards grouping. When they involute they may disappear without leaving a trace, they may leave some pigment, or more rarely depressed scars.

The lenticular lesions may also become corymbose, just as the miliary papules may, although it should always be borne in mind that this form is not common.

The hypertrophic lesions may be distinctly fungous, then forming the frambesiform type of syphilis. These lesions are most apt to develop around the mouth or nose, in the axillæ, and in the anal or genital region. In size the papules may be an

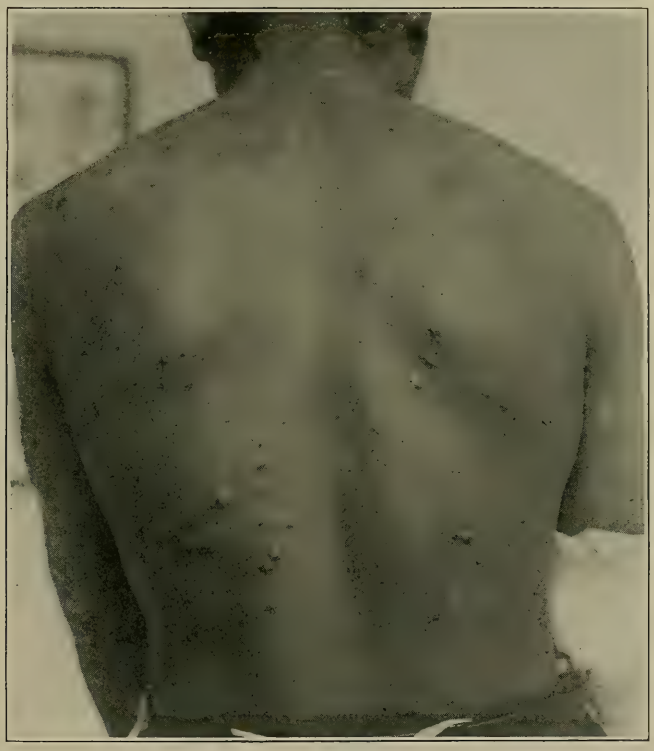

Fig. 30.—The lenticular syphilides stand well up above the level of the skin.

inch or even more in diameter, and are often distinctly verrucose, closely resembling the lesions of yaws. As a rule the odor is very offensive. Curiously enough these lesions usually fade away rather promptly under antisyphilitic treatment. It is probable that the hypertrophic lesions are usually composed of a number of papules that have coalesced.

The confluent lesions may be extremely large, sometimes attaining a diameter of an inch. As a rule it is easy to distinguish the separate papules. There seems to be no particular location where confluence is most apt to occur, for as a rule confluent lesions may be found scattered over the trunk and limbs.

Fig. 31.—In lenticular syphilis the lesion may fuse.

The lenticular lesions but rarely become squamous.

The pathology of these lesions has been studied by Fordyce, Unna, Dennie, Crocker and others, as has already been mentioned, and there is general agreement as to the findings. There is a circumscribed lesion consisting of lymphocytes, plasma cells and

proliferated fibroblasts which frequently surround the vessels like a coat sleeve. Giant cells are far from uncommon. There is also an endarteritis of many of the vessels. The perivascular infiltration undoubtedly starts in the perivascular lymphatics. The changes in the epidermis are secondary. It may be thinned from pressure of the granuloma beneath, or there may be edema with an increase in thickness and scaling.

These lesions must be diagnosed from papular eczema, psoriasis, lichen planus, scabies and erythema multiforme. The diag-

Fig. 32.—Frambesiform or hypertrophic syphilides are rather unusual.

nosis of eczema and psoriasis from syphilitic lesions has already been discussed. Lichen planus presents angular lesions with flat tops, that often show umbilication and which shine by reflected light. In addition they are usually arranged in rows. In the later lesions the violaceous color is very characteristic. There is frequently extreme itching. Lesions in the mouth should always be looked for. The distribution of scabies, the multiform types of lesions and the itching at night should serve to distinguish this disease. It will be recalled that the lesions pre-

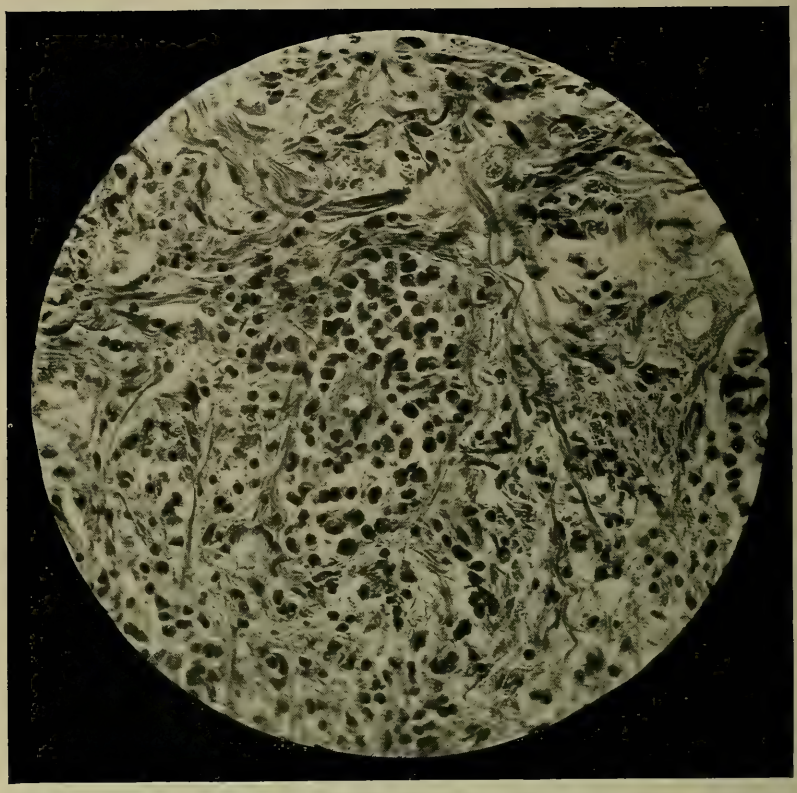

Fig. 33.—In the early skin lesions of syphilis there is a characteristic perivascular infiltration with small round cells and plasma cells. (Collection of Drs. Fordyce and MacKee.)

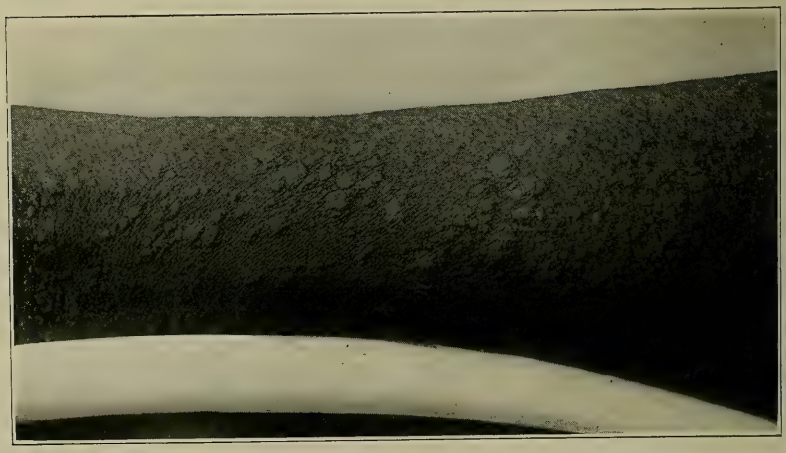

Fig. 34.—The lesions of lichen planus may resemble the papules of syphilis, but closer inspection shows them to be angular, umbilicated and arranged in rows.

A.

B.

Fig. 35.—The lesions of erythema multiforme are most frequent on the backs of the hands. They tend to be annular, sometimes form almost perfect rings (as in the upper figure).

dominate between the fingers, upon the flexor surfaces of the wrists and elbows, in the axillæ, over the buttocks and lower abdomen, and upon the inner surfaces of the thighs, while the face is spared. In women lesions are found beneath the breasts and in men upon the genitals. The lesions are papular, vesicular and pustular. The diagnosis of erythema multiforme has already been discussed.

Fig. 36.—The discoid syphilides are almost characteristic.

Discoid Papular Syphilide

By discoid papular syphilides are meant those that are flat, and which do not protrude to any extent above the surface of the skin. The disseminate lesions are scattered over the entire cutaneous surface. The face, neck, and frequently the palms and soles are affected. On the latter the lesions are scaly and flat. The lesions are more marked upon the flexor than upon the extensor surfaces of the limbs, and are usually more frequent upon the back than upon the chest and abdomen. The lesions

are circular or roughly oval in shape and are well defined. In size they vary from one-fourth to nearly two inches in diameter, although the primary lesions are never more than one-half inch in diameter. The center is often a trifle depressed. They present the usual variations in color. As a rule they are more or less covered by scales. They may occur along with the lenticular lesions, but this is not usual. In the negro these lesions not in-

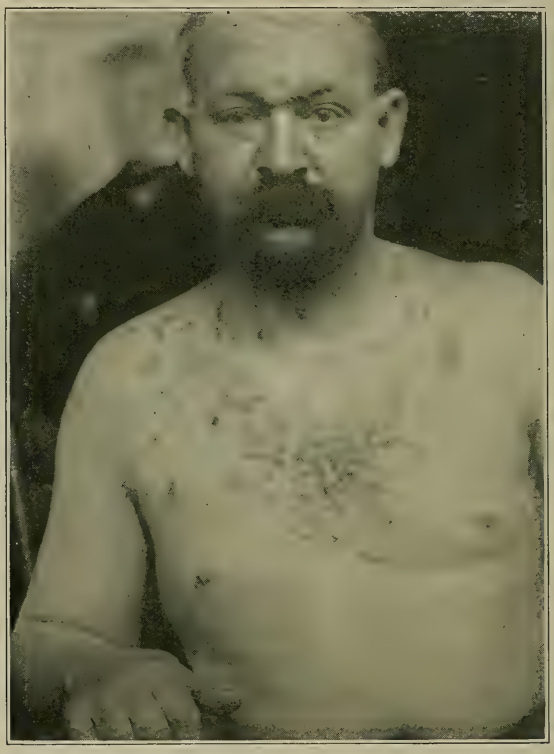

Fig. 37.—In this instance the large discoid papules were sharply localized.

frequently become annular as has been pointed out by Atkinson,[17] Gilchrist,[18] Howard Fox[19] and myself.[20] The annular lesions are most common around the angles of the mouth and eyes and upon the chin, but they may occur upon any portion of the body, except the palms and soles. At times they may be found upon the mucous membranes. There may be but one annular lesion or there may be hundreds. They are usually not found upon the

limbs, but may occur there. The lesions form from the peripheral extension of a papule with central absorption. In some cases

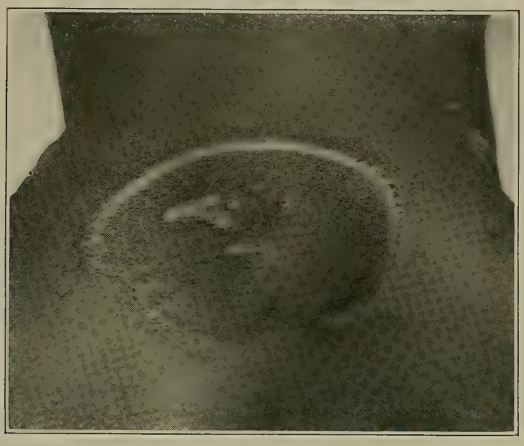

Fig. 38.—In the negro discoid papular lesions frequently become annular.

Fig. 39.—Annular lesions are most frequent around the mouth. (Collection of Dr. T. Caspar Gilchrist.)

a marked scale formation may take place in the center, in others the center consists of normal skin. There may be either an

increase or a decrease in the amount of pigment present, or it may be unchanged. In some instances rings are formed within rings, and in others the coalescence of lesions gives rise to gyrate patches. These lesions must not be confused with the neurosyphilides or with the late serpiginous lesions which are really gummatous in character. In exceptional cases members of the white race may show similar lesions, illustrations of which may be seen in many of the atlases. Pathologically these lesions are

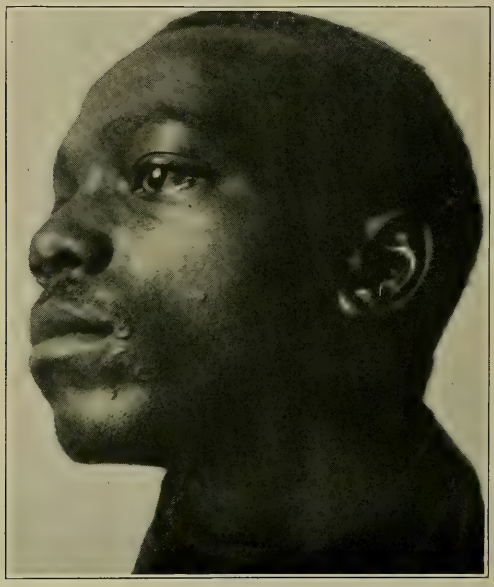

Fig. 40.—Annular lesions may be either few or numerous.

characteristic of syphilis, except that the perivascular infiltrate is not as heavy as one would expect. These annular lesions must be distinguished from ringworm, pityriasis rosea, psoriasis, seborrheic dermatitis and erythema multiforme. The lesions of ringworm are more inflammatory, some vesicles are usually present at the margins, they are not so infiltrated nor are they so symmetrically situated. Upon microscopic examination the parasite can readily be demonstrated. The lesions of pityriasis rosea do not develop upon the face except in rare instances, but predominate upon the trunk. The lesions are rather more inflammatory

than are the annular syphilides, and can usually be recognized by the fact that they are distinctly oval and that their long axes are parallel with the direction of the ribs. They vary much in size and are scaly from the inception. Then, too, there is usually a large parent lesion. Psoriasis does not occur upon the face,

Fig. 41.—Annular lesions are always characteristic.

the lesions usually predominate upon the extensor surfaces, and upon the trunk, while lesions are common in the scalp. The scales are profuse, white and feathery and there is no deep infiltration. Psoriasis is usually chronic, or at least gives the history of recurring attacks. Seborrheic dermatitis is usually found in the axillæ and groins or in the midline of the back or chest.

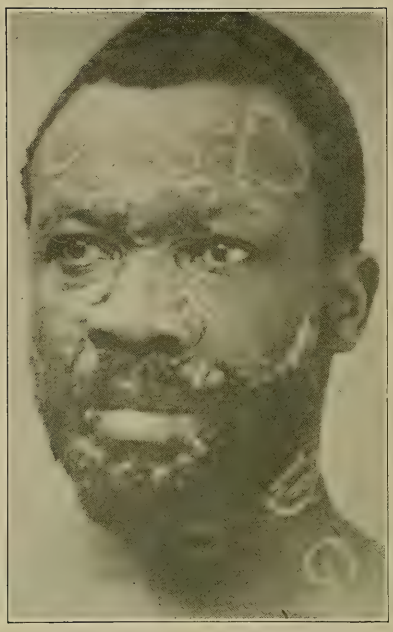

Fig. 42.—Rings may form within rings. (Collection of Dr. T. Caspar Gilchrist.)

Fig. 43.—The discoid, squamous lesions of early syphilis may tend to become annular.

The lesions have a yellowish cast and usually itch slightly. They are superficial and there is but little infiltration. The scales are rather greasy and are not closely adherent. There are no other signs of syphilis. The lesions of erythema multiforme are apt to predominate upon the hands and forearms. They are never scaly, and there is generally the history of recurring attacks.

The confluent lesions follow the same course as those of the confluent lenticular syphilides.

The papulosquamous lesions may affect any portion of the body, but as a general rule this type of lesion is more or less localized to symmetrical areas, and typical papules can be found in other areas. However, in some instances there is no other type of eruption and the disease may then readily be mistaken for psoriasis. In syphilis, however, the scales are more closely adherent and there is more infiltration. The lesions are apt to predominate upon the flexor rather than upon the extensor surfaces, while the reverse is true of psoriasis. The concomitant signs of syphilis are of great value in making a correct diagnosis.

The moist patches or condylomata lata are usually of a later development than the other secondary manifestations, and may appear many years after the date of the initial sclerosis. They are much less frequent in the cleanly than in the dispensary class. They are more common in women than in men and are more common in negroes than in whites. The fact that all syphilitic negro women suffer from them at some time may help to explain the greater prevalence of the disease in this race, for the lesions simply swarm with organisms, and are consequently very infectious. The moist papules are simply papules which have been modified by their environment, namely, heat, moisture and pressure. They are occasionally seen under the breasts of women but are most common around the anus, on the vulva, and in the perineum. Rarely they may be seen upon the mons veneris or upon the scrotum. The lesions vary from one-third to three-quarters of an inch in diameter, and are either round or oval. There may be but two or three lesions or there may be many. The edges are sharply defined and the edges rise at right angles from the skin and the top is flat and covered with a grayish necrotic membrane that is more or less glistening. At times the lesions may be hypertrophic and then resemble the frambesiform

ones already described. The term "condyloma" is used loosely by many men to refer to the ordinary venereal warts, but should always be reserved for the true syphilitic lesions. Patholog-

Fig. 44.—Discoid, squamous lesions may resemble psoriasis. (Collection of Dr. Robert G. Washburn.)

ically the lesions resemble the ordinary papular syphilides, but in addition there is a great development of the epidermis the downgrowths of which are much deeper and broader than usual.

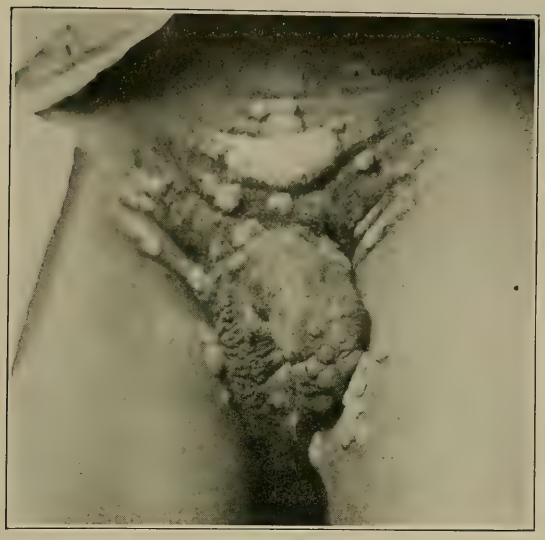

Fig. 45.—Condylomata are simply moist discoid papules.

Fig. 46.—Condylomata may occur around the anus at almost any time during the course of syphilis. (Collection of Dr. Richard L. Sutton.)

Typical condylomata can be mistaken for no other disease, but when they are more or less fungous they may resemble venereal warts. However, some typical lesions can usually be found, so that the diagnosis should not be difficult in the vast majority of instances. The laboratory findings or other signs or symptoms of syphilis should serve to exclude the few doubtful cases which do resemble venereal warts.

Fig. 47.—In the unclean, condylomata may become hypertrophic. (Collection of Drs. Fordyce and MacKee.)

Papulopustular Syphilide

The papulopustular lesions are not infrequent, especially in the negro. The small acuminate lenticular papules are most subject to undergo pustulation, but as a rule only a small number of the papules are affected, and chiefly those upon the flanks and ex-

tensor surfaces of the limbs, especially the legs. The pus formation takes place near the apex of the papule and may remain almost microscopic or may affect almost the whole papule. The pus is usually thick and creamy and contains staphylococci. Among syphilographers the statement is generally made that pustular syphilis is most apt to affect the cachectic or the poorly nourished, but this is certainly not the case in the negro race,

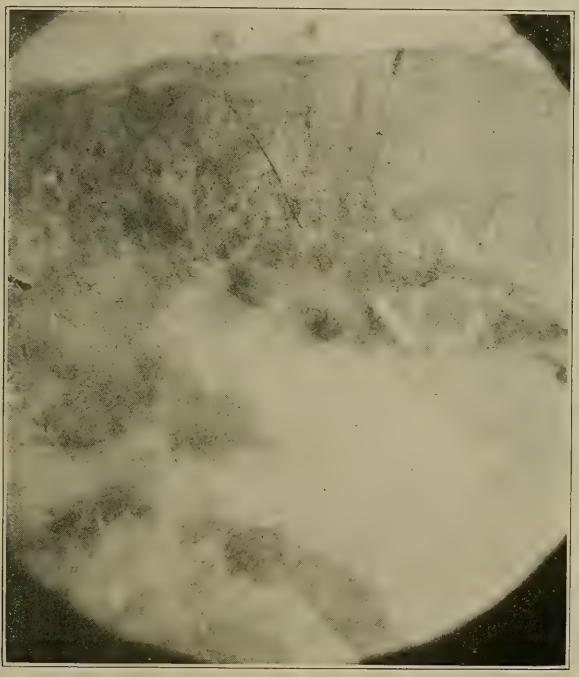

Fig. 48.—In papular syphilis there is frequently heavy perivascular infiltration.

for, as a rule these cases do not run a severe course in this race, although in the whites they may do so.

Pustular Syphilides

There are two clinical varieties of acuminate pustular syphilis, the very superficial and the more deeply situated. In both instances a papule is the original lesion. The former variety are comparatively common in the negro, but very rare in the white. They are usually situated upon the flanks and outer surfaces of

the thighs, but may occur upon any portion of the cutaneous covering. The individual lesions are discrete, superficial pustules, not over one-third of an inch in diameter, and often smaller. The roof of the pustule is thin, but the lesions do not rupture

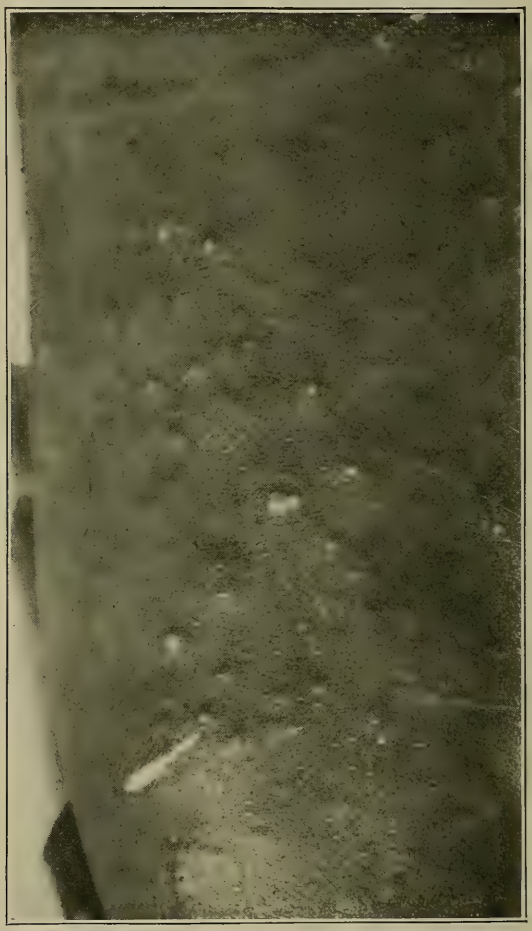

Fig. 49.—In papulopustular syphilis there may be creamy pus.

early. They are filled with creamy pus. These syphilides must be differentiated from chicken pox and from a dermatitis venenata. In the former the lesions are distinctly vesicular and rupture early, and in the early stages there is often a wide

inflammatory areola. Other signs of syphilis are lacking, and there are usually more lesions upon the face. Dermatitis venenata does not have the symmetrical distribution of syphilis and there is more itching and burning.

The deeper lesions are more widely disseminated, the face

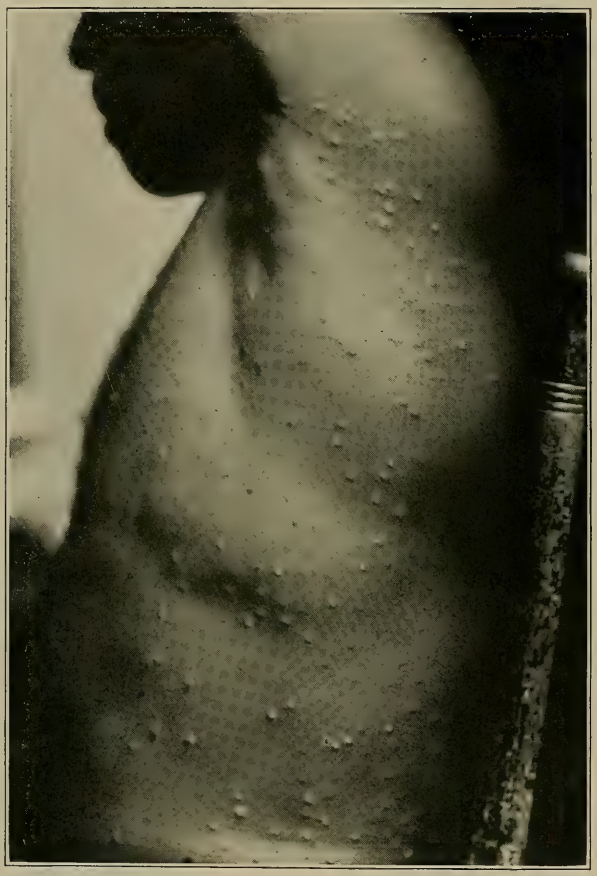

Fig. 50.—The pustular syphilides may be extremely superficial.

being a favorite site for them. In addition the flanks and thighs are usually markedly affected. In almost all instances there is a varying admixture of papules. These lesions usually heal rather slowly under treatment, and are apt to leave deeply pigmented spots upon the skin, and at times true scars may result.

They must be differentiated from smallpox and from a drug rash and occasionally from acne vulgaris. Smallpox usually comes on abruptly with fever, backache, headache, vomiting and the history of some antecedent chilliness. The lesions are most numerous upon the face and hands, and there are almost always a few lesions in the palms. They usually occur in the unvaccinated. The course of variola is different, inasmuch as the lesions pass through a certain definite course, papule, vesicle, then pustule, and the vesicle stage usually lacks in syphilis. The

Fig. 51.—Ecthymoid pustules may be very difficult to differentiate from gummata: in some instances there is no hard and fast dividing line. These lesions came on less than four months after the chancre.

lesions themselves are often very similar and it may be unsafe to make a diagnosis from the cutaneous picture alone, although the distribution is usually a great help. The presence of other signs of syphilis, either laboratory or clinical, is of great value in establishing a proper diagnosis, although it must always be borne in mind that variola may attack a syphilitic individual.

Pathologically the abscess cavity forms in the upper portion of the rete, usually just beneath the granular layer. The cavity is filled with polymorphonuclear leucocytes and some few small round and plasma cells. The picture in the corium is essentially the same as in papular lesions, but there are numerous leucocytes in addition to the more common types of cell.

The obtuse pustules of syphilis usually occur in connection with some other types of lesion, being especially frequent upon the back and shoulders. At times they may be generalized. The occurrence of a few has no especial significance, but the generalized form is usually the sign of a lowered resistance to the treponema, either due to allergy or to a bad general condition. The lesions may begin either as macules or papules, although some authors state that they may be pustular from their inception. In size they vary from one-eighth to one inch in diameter, and they are roughly round in shape. At the onset they are somewhat elevated with a thin roof, which soon becomes flaccid and which ruptures early. Then a scab is formed beneath which is a punched-out ulcer, often of considerable depth. Surrounding the scab is a slight inflammatory areola, that frequently has a livid or even a bluish tint. As a rule these lesions leave but a small scar when they heal, although pigmentation frequently follows them. They must be differentiated from ecthyma and impetigo contagiosa. Ecthyma usually occurs upon the legs, and in typical cases is much more inflammatory than is syphilis. In ecthyma the ulcers beneath the crusts are superficial and are not distinctly punched out. Impetigo is almost never a widely spread disease, and the usual site of the lesions is on the face, the chin being especially affected. When the scab is removed there is no ulcer beneath, simply a raw area. Other signs of syphilis are lacking in both of these diseases.

The ecthymoid pustules are accompanied by a moderately deep and circumscribed ulceration, considerably like that of a broken-down gumma. They are signs of allergy. They are most frequent upon the anterior aspects of the legs, but may affect any portion of the body. In some instances the entire bodily surface is covered with such lesions, but this is very unusual, and is spoken of as malignant syphilis. The lesions are covered by a dark brown crust, which tends to become thicker due to new

deposits upon its lower surface. When the crust is removed, a punched-out ulcer is plainly evident. The walls of this ulcer run at right angles to the skin and descend fairly deep down into the corium. The base of the ulcer is usually covered with a tightly adherent greenish secretion, beneath which are unhealthy looking granulations. There is frequently a purplish red areola for a considerable distance around the lesion. At times these lesions respond readily to treatment, but in some cases they are very refractory.

Pathologically the picture is practically identical with gumma, which will be described in the following chapter.

These lesions must be distinguished from ecthyma, but the diagnosis can be made as indicated above.

In certain instances the crusts covering the pustular lesions are built up from beneath by larger and larger deposits, so that a laminated crust results, which is conical in shape. This condition is spoken of as a rupia, and was once believed to be of grave prognostic import.

In still other instances there is practically no crust and the lesions appear simply as punched-out ulcerations, several of which may fuse. This type is frequently very resistant to medication. Pigmented scars result from all lesions of this type. Furunculosis has been mistaken for this last mentioned condition, but the chronicity of the lesions, together with the punched-out character of the ulcers should save the clinician from falling into this error.

Vesicular Syphilide

While it is universally conceded that vesicular and bullous lesions are not infrequent in congenital syphilis, still many authors, including George Henry Fox,[21] claim that they do not develop in the acquired form of the disease. In regard to this point Ormsby[22] well observes: "It is thought that the larger number of these lesions are either immature pustules, exanthematous lesions in syphilitic subjects, or pure accidents of the syphilitic process. With regard to the first theory it may be said that the pustular syphiloderm not rarely begins as a vesicular lesion; with regard to the second that the coincidence of so common a disease as syphilis with other cutaneous disorders

is a matter of frequent observation; and with regard to the third, bearing in mind the large quantities of potassium iodide taken for the relief of the disease and its capability of exciting a vesicular eruption, it can reasonably be concluded that some at least of the cases of so-called vesicular syphilis have been imperfectly studied. That a true syphilitic lesion represented by bullae does occur there can be no doubt, but it is unusually rare." For a more lengthy discussion of this problem the reader is referred to the discussion of Fox's paper.

Bullous lesions are likewise extremely rare; however, they may occur upon the extremities, and be indolent in their course. As a rule they occur early in cachectic subjects. They must be distinguished from pemphigus and bullous erythema multiforme.

Neurosyphilide

The "neurosyphilide" of Unna,[23] or the annular macular syphiloderm is an uncommon type of lesion that may appear in from six weeks to two years after the initial lesion. The lesions

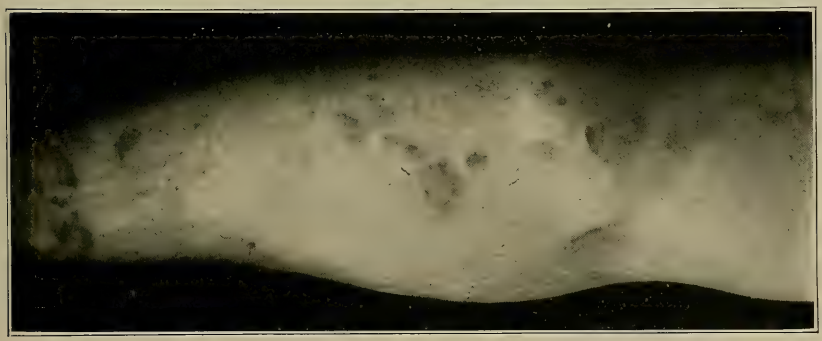

Fig. 52.—The "neurosyphilide" of Unna is believed to be due to nerve involvement rather than to the local action of the treponema upon the skin.

are stated by Unna not to show any of the histologic picture of a syphiloderm, but to be due to syphilis of the nerves, and to be a trophic disturbance comparable to the anesthetic type of leprosy. While this work has never been confirmed, there can be no doubt that there is a type of lesion that almost exactly resembles erythema multiforme, for the lesions are circular, but slightly raised, do not scale, give rise to no subjective disturbances, and are very chronic. They disappear but slowly under

specific treatment. Their chronicity and the findings of other evidences of syphilis serve to distinguish them from erythema multiforme, seborrheic dermatitis and ring worm. Howard Fox[24] has recently reported a case.

In addition to the lesions already described, there are a number of rare forms. For instance, any of the lesions may become hemorrhagic. At times papular lesions upon the legs may be so numerous that they will fuse giving a picture strongly suggestive of ichthyosis.

Relapsing secondary lesions may be of any of the types already described, but the commonest are the macular, the papular and the pustular. The two latter are rather prone to occur in groups, and may form definite rings, especially in negroes. These recurrent lesions may occur at any time from two weeks to many years after the disappearance of the original secondary eruption, and are due to a septicemia.

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CHAPTER VII

LATE CUTANEOUS LESIONS

The classification proposed by George Henry Fox[1] and adopted by the American Dermatological Association will be followed in discussing the late cutaneous lesions of syphilis. It should be clearly understood that in the late stages of syphilis there may be found typical early syphiloderms, but as a general rule the late cutaneous manifestations fall under one of the following heads.

Nodular	Agminate—confluent, squamous, cicatricial. Circinate or Serpiginous—squamous, crustaceous, ulcerative, cicatricial.
Squamous	Circumscribed. Diffuse.
Gummous	Diffuse—verrucous, crustaceous, rupial, ulcerative. Tuberous—ulcerative, cicatricial.

Fox separates the circinate from the serpiginous nodular lesions, but I can see no necessity for this. It is also somewhat questionable whether the squamous lesions should be subdivided, for both are simply different stages of the same process. Fox uses the expression "nodular" rather than "tubercular" for the good and sufficient reason that the latter has been found confusing by many students, who will persist in thinking that the tubercle bacillus must play some part in its development. Likewise the word "gummous" is given preference over the older "gummatous."

Nodular Agminate Syphilide

The nodular agminate syphilide is one of the common tertiary manifestations of syphilis. It may develop within one year after infection, or it may not appear for many years. The lesions are usually limited to comparatively small areas of the skin, but may exceptionally occur in many places. The sites of predilection are the forehead, chin, neck, buttocks and outer aspects of the

thighs. The lesions tend to occur in groups, often in circles, or in horseshoe- or kidney-shaped patches. In color they vary from

Fig. 53.—Agminate nodules are common upon the face; eventually they usually ulcerate.

Fig. 54.—In this instance an agminate nodular lesion resembled a cancer; diagnosis was rendered more difficult by a negative Wassermann.

a pale pink to a deep purplish red. The diameter of the individual lesions varies from one-eighth to one inch. The shape of

the primary lesions is roughly circular. They can be felt to be situated in the corium, with adherent skin covering them. They

Fig. 55.—Agminate nodules of syphilis frequently resemble cancer.

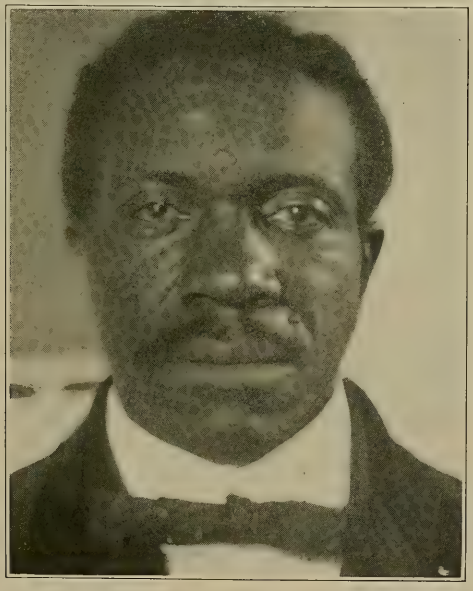

Fig. 56.—Agminate nodules may be mistaken for leprosy as in this instance.

are firm and sharply circumscribed. The surface may be smooth or may desquamate. These lesions rarely show pustulation. In

many instances these lesions break down, forming punched-out ulcers, but this is by no means always the case, for they may persist for a year or more without showing any signs of necrosis. Frequently they are slowly absorbed, either with or without scar formation. It should be especially noted that these lesions may be so mild and occasion so few symptoms that the patient fails to notice them, and it is very frequent for the physician to fail to diagnose them correctly. I have seen them mistaken for urticaria, eczema, fibromata, lipomata, sebaceous cysts, in fact for any type of nodular lesion, but the lack of subjective symp-

Fig. 57.—Agminate nodules may become confluent. (Collection of Dr. T. Caspar Gilchrist.)

toms, the cold color, the firmness and the chronicity should usually render the diagnosis easy for one who has had a few pointed out to him.

The circinate and serpiginous nodular syphilides often form very striking pictures. At first they arise as do the agminate lesions, except that they elect the limbs and buttocks and more rarely the trunk upon which to arise. Upon the face they are very rare. Usually a number of grouped nodules appear, these extend peripherally, fairly rolling outward as it were, leaving behind either a thin scar, a typical deep ulceration, or normal

skin that appears to be changed only in the amount of pigment, which may be either increased or diminished. There may be a combination of types. It is not infrequent to find patches a foot or even more in diameter. At times there may be only a few

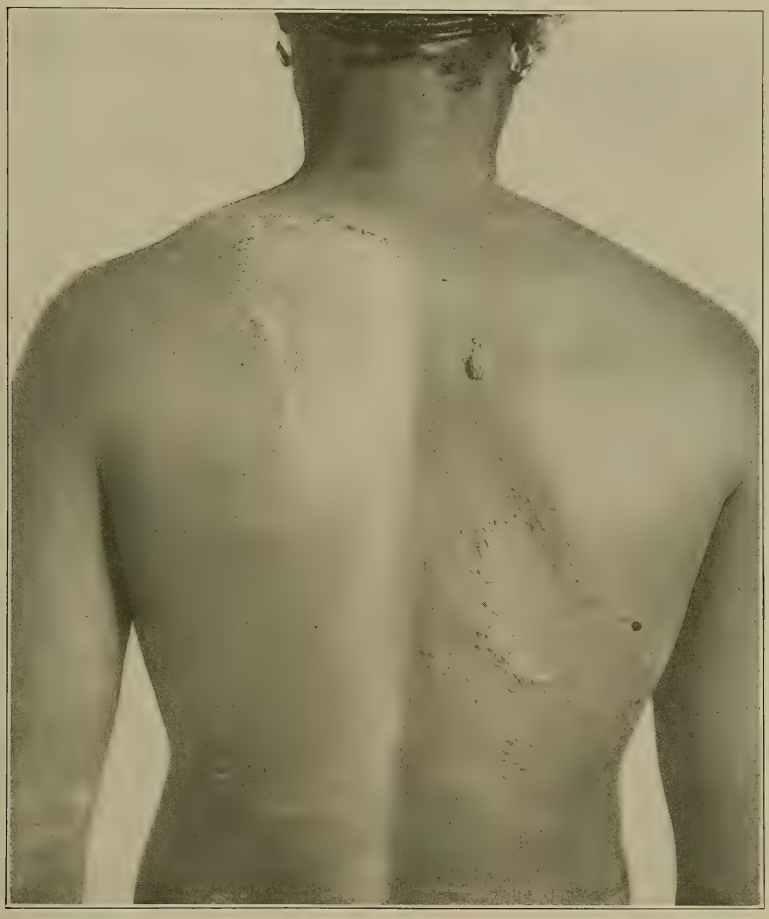

Fig. 58.—Serpiginous nodular syphilis is characteristic. (Collection of Drs. Fordyce and MacKee.)

nodules to mark the advancing edge, but in other instances there is a steady chain of nodules that resemble a chain of beads, varying only in that some are confluent. When the nodules are close together there is more tendency for the formation of either

punched-out ulcers or atrophic scars than when a smaller number of nodules are present. In all instances the spread is comparatively slow, it usually taking at least three months for a lesion to reach a diameter of six inches. While the early lesions of syphilis are usually symmetrical, it is unusual for this to be true of the late ones. Then, too, in the late lesions there is a tendency for the syphilides to disappear spontaneously, only to crop up on some other portion of the body.

Pathologically all of the nodular lesions show striking similarities. Fordyce[2] gives the following description: "In the

Fig. 59.—A circinate nodular syphilide may form rings within rings. (Collection of Dr. Richard L. Sutton.)

nodular or tubercular syphilide the entire cutis from the epidermis to the subcutaneous fat tissue was involved, under a low power showing alternating light and dark areas, the former representing the altered blood vessels and the latter a cellular effusion. Under the high power the infiltration was composed of plasma and giant cells, lymphocytes and hyperplastic fibroblasts. The vessels, increased in number, showed the effects of an obliterating endarteritis, their former site being marked by solid cords, groups of irregularly disposed cells with pale staining nuclei and giant cells with peripheral or central nuclei or both. Near the edge of the section were a few vessels with narrowed lumina and a hyperplasia of all their coats. A number of

the lymph spaces were thrombosed. The few remaining bundles of connective tissue had here and there a vacuolated appearance, the result probably of a fatty degeneration and beginning regression. The epidermis was flattened out into a very thin band."

The diagnosis of the serpiginous lesions must be made from

Fig. 60.—Late papulosquamous syphilides, in fact all late syphilides, have the same characteristic structure as the earlier lesions of syphilis. (Collection of Drs. Fordyce and MacKee.)

lupus vulgaris, lupus erythematosus, leprosy, mycosis fungoides, epithelioma, rosacea and psoriasis. Lupus vulgaris very rarely commences in a patient over twenty years of age, and is distinctly rare in America. As a rule there are but one or two lesions, and these have a great tendency to be on the nose or face, much more rarely on the limbs or body. The lesions spread very slowly, it

usually taking a year for a diameter of an inch to be reached. Lupus nodules can sometimes be seen as small "apple-jelly" colored spots near the edge of the lesion. It is usually stated that the scars resulting from lupus lesions are more superficial and of finer texture than are scars from a syphilide, but I should hesitate to put too much stress on this point. Lupus erythema-

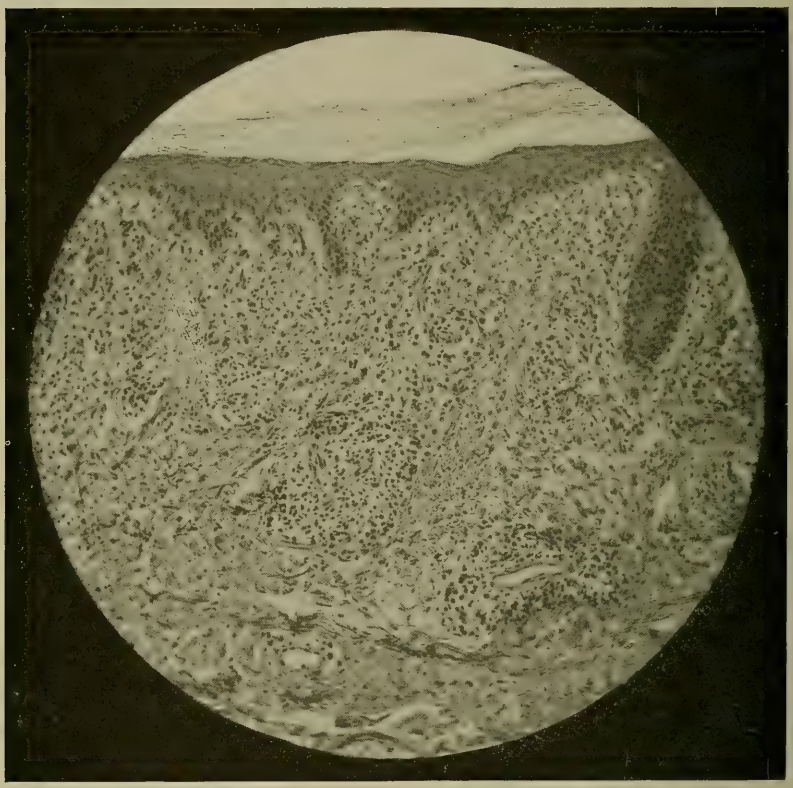

Fig. 61.—Under high power the characteristic perivascular infiltration can easily be recognized. (Collection of Drs. Fordyce and MacKee.)

tosus never ulcerates and never forms marked nodules. The lesion is usually covered by adherent white scales beneath which a dilated follicular mouth can be seen. The lesions generally occur upon the face, tend to be symmetrical, and grow but slowly. The lesions of lepra are usually more indolent than are the syphilides and are apt to have an "oiled look," lacking the livid or

dull crimson color so characteristic of syphilis. The laboratory methods will show the presence of lepra bacilli in large numbers.

Fig. 62.—The nodular syphilides show massive perivascular infiltration. (Collection of Drs. Fordyce and MacKee.)

Mycosis fungoides begins with eczematous-like lesions that itch intensely, later large tumors develop rapidly. Epitheliomata of

the basal-celled variety almost always develop from precancerous lesions, frequently a seborrheic keratosis, and are most common on the face. They grow very much more slowly than do syphilides and practically always have a hard-rolled edge usually of a pearly white color. They but rarely produce punched-out ulcers. The granulation tissue is extremely friable. In

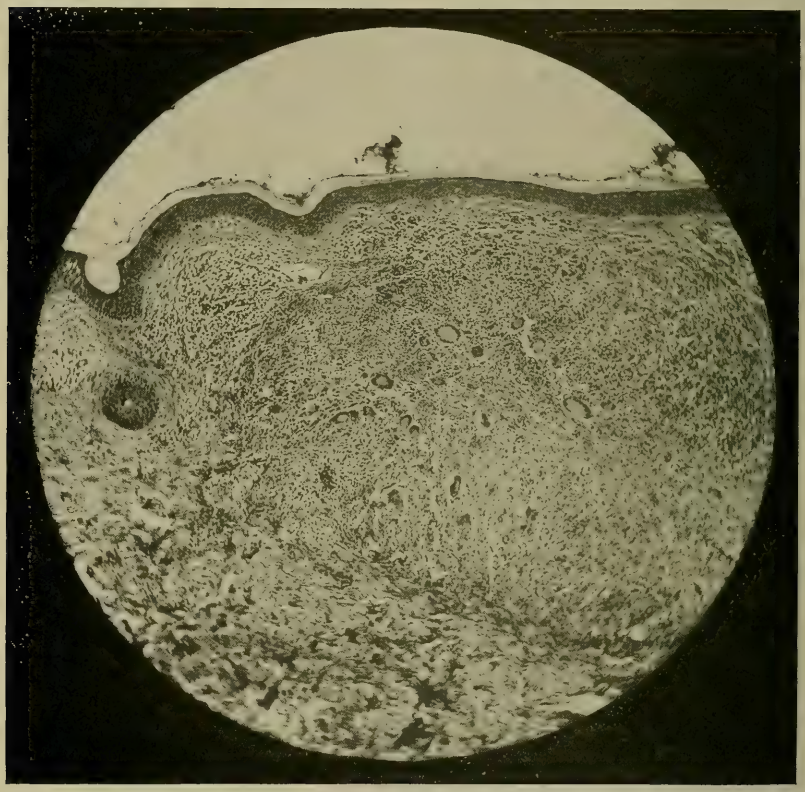

Fig. 63.—At times numerous giant cells occur in the late nodular lesions. (Collection of Drs. Fordyce and MacKee.)

rosacea there is no scarring produced, and the lesions are limited to central portions of the face. The history of an antecedent redness of the face is important, although, of course, syphilis may occur in one who also has rosacea. The presence of numerous dilated blood vessels is of considerable importance, as these usually do not occur in syphilis. Psoriasis never forms scar tis-

sue, and lacks induration. The scales are fine, and when removed, leave minute bleeding points. As already pointed out, the distribution is characteristic, for the lesions usually predominate upon the extensor surfaces and are not infrequently found in the scalp.

Gummous Syphilides

Gummous (gummatous) lesions are usually late manifestations of syphilis. As already pointed out they are due to allergy

Fig. 64.—Broken-down gummata may be multiple; the leg is a common site.

on the part of the host. If the victim suffers from an early allergy, these lesions may appear at a very early date. As a rule, however, they do not appear until at least two years have expired from the date of the initial infection. When they appear they are apt to be numerous and roughly symmetrical, but when they develop later, they are usually asymmetrical and few in number. As already pointed out gummata may appear in any portion of the body: upon the skin they are most apt to occur upon the upper half of the lower leg, upon the face, trunk, arms and scalp, but may appear anywhere. There is a tendency among

students and many practitioners to regard a lesion as gummous only after it has broken down and produced an ulcer, but of course this is incorrect, inasmuch as ulceration is simply a later stage of the gummous process. A gumma develops as a firm, circumscribed, mildly inflammatory nodule in the corium, although, of course, a periosteal gumma may ulcerate through the skin. There is usually but little pain and but a slight amount of tenderness associated with its development. The nodule slowly increases in size, although at times this growth may be very

Fig. 65.—Solitary gummata are usually larger than are multiple ones. Note a ringed lesion just beneath the lip.

Fig. 66.—The scalp is a frequent site of gummata: they usually spring from the bone. (Courtesy of Dr. John W. Perkins.)

rapid, until a diameter of from one-half to nearly two inches is reached. Then central softening usually develops, and following the course of least resistance breaks through the skin, so that a deep punched-out ulcer is formed. When the lesion ruptures, a thick gummy fluid is discharged, and it is from the character of this discharge that the name "gumma" is derived. If secondary infection occurs, the discharge may be frankly purulent. The resultant ulcer is usually characteristic: it is either round, oval or kidney-shaped, deep, with the walls descending at right angles from the skin so that the name "punched-out" is given. The base is covered by a thick tenacious secretion. A number of other gummata are apt to arise

in the immediate neighborhood and the resulting ulceration may then be very large, so that it may be many inches in diameter. Around the ulcer there is always an indurated area with a reddish or purplish areola upon the skin. At times these lesions are covered by crusts that vary considerably in thickness. These crusts may be rupial, or they may be thin, when they are called crustaceous. In rare instances there may be proliferation of

Fig. 67.—When a gumma breaks down a characteristic "punched-out" ulcer is formed. (Collection of Dr. Richard L. Sutton.)

tissue so that a verrucose appearance results. These lesions eventually heal by the formation of granulation tissue in the base, and the later development of a scar. As a result of this scar formation there may be varying degrees of contracture. Gummata usually heal rather readily under proper antisyphilitic remedies.

Before ulceration gummata must be distinguished from furuncles, erythema nodosum and erythema induratum, more rarely from neoplasms. From furuncles they may be differentiated by milder inflammatory reactions, their slower course and the slight pain that they produce. In case of doubt, aspiration and the examination of the contents may help to decide the question, as furuncles contain polymorphonuclear leucocytes and gummata do not, unless secondarily infected. Erythema nodosum has multiple symmetrical nodes, usually upon the legs, that are fre-

Fig. 68.—In exceptional instances a gumma may have undercut edges.

quently associated with erythema multiforme-like lesions in the same locality. There is usually some fever, malaise and arthritic pains, and a general "grippy" condition. The nodes practically never ulcerate. The lesions of erythema induration or Bazin's disease are due to a mild tuberculous process, and are usually symmetrical, commonly upon the lower portion of the calves. This disease chiefly affects young girls, especially those who are much upon their feet. The lesions usually are smaller than are the gummous syphilides, but this is by no means always true.

The symmetrical character of the lesions, the absence of other signs of syphilis and the failure to heal under antisyphilitic medication is diagnostic. Neoplasms usually develop much more slowly and are not so inflammatory.

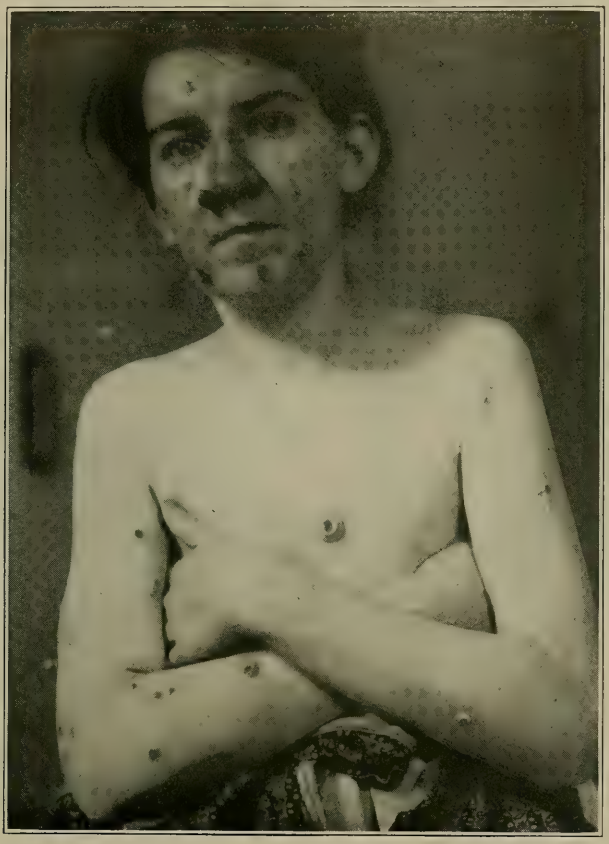

Fig. 69.—Rupial crusts are not especially common. (Collection of Dr. Robert G. Washburn.)

After ulceration several diseases must be differentiated: namely, varicose ulcers, tuberculous ulcers, carcinomata, sporotrichosis and traumatic ulcers. Varicose ulcers arise only upon the lower third of the legs, and usually near the ankle. They are always accompanied by varicose veins, either deep or more frequently superficial. The ulcers are not deep as a rule and are

often accompanied by an eczema of the surrounding skin. There are no other signs of syphilis, although such ulcers may occur in syphilitic patients. Tuberculosis of the skin practically always starts in persons under twenty years of age, and the lesions are most commonly situated upon the face, especially the nose. They remain constant; do not come and go the way syphilitic lesions are prone to do. Their spread is always slow, it taking months before any considerable size is reached. The lesions are not punched out, the skin overhangs the edges, and there are no other signs of syphilis. It should always be remembered that this condition is distinctly unusual in America. Also it is difficult to demonstrate the tubercle bacilli in the lesions. Cutaneous

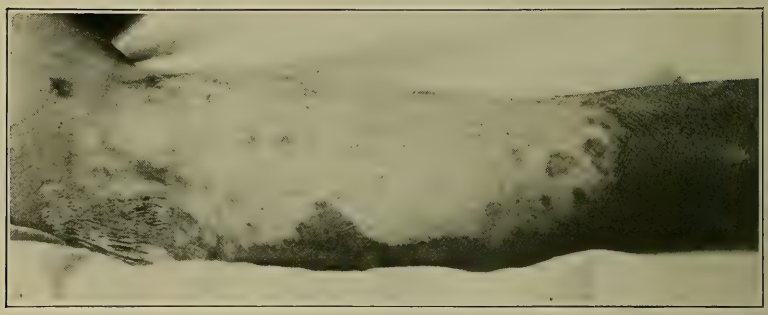

Fig. 70.—When ulcerative lesions heal, a smooth white scar is the usual result.

cancers but rarely show a punched-out appearance, neither do they show an inflammatory areola. The edge is practically always hard, and may show definite pearly nodules. The base is covered with friable granulation tissue, that bleeds readily on slight trauma. They practically always arise from definite precancerous lesions. The ulcers of sporotrichosis begin as do syphilitic ulcers and often closely resemble them, but always develop in a row along a lymphatic chain. In addition there are frequently sinuses that rupture through the neighboring skin. At times the causal organism can be found in the discharge. Other evidences of syphilis are lacking. Traumatic ulcers are usually shallow, often irregular in shape, and are not preceded by subcutaneous nodes. They heal readily under local treatment.

Diffuse Gummous Syphilides

In addition to the circumscribed forms of gummata there is also a diffuse form in which the skin and hypoderm are infiltrated to varying degrees of thickness. These lesions are most common upon the limbs and buttocks, but may occur upon any portion of the skin. There may be but one patch or there may be several, and other clinical evidences of syphilis may be present or absent. In size the lesions vary from a diameter of one inch to very extensive patches, that may be over a foot in diameter. The edge may be either sharply or poorly defined, but is always convex. The color varies from a pale pink to a deep purplish red. There may be no ulceration, which is the more common form, or the entire area or portions of it may be the site of ulcerations. Eventually the whole patch may break down. The

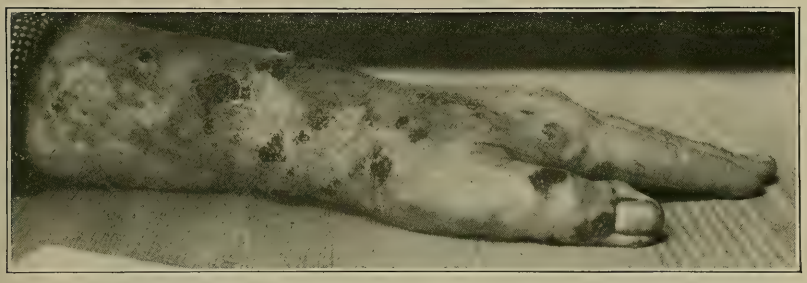

Fig. 71.—Diffuse subcutaneous infiltrations frequently end in localized ulcerations.

configuration of the lesions may be circular, oval, serpiginous or irregular. At times an elephantiasis may result. The infiltration is the chief aid in the diagnosis where no ulceration occurs. However, various other skin diseases must be differentiated, notably psoriasis, eczema, erythema perstans, Bazin's disease, lupus erythematosus and the psoriaform type of lupus vulgaris. Leprosy also may be simulated. All of these can be excluded by the rules already laid down.

The pathology of the gummous lesions has been well described by Fordyce, who states: "The gumma comprises the derma throughout its entire extent with marked vascular changes, a diffuse infiltration and necrotic foci. Viewed with low power, there was apparently a decrease in the number of blood vessels,

but on careful examination it was found that many were obliterated or had their caliber reduced and their walls thickened. The infiltration consisted of lymphocytes, plasma cells and a large number of hyperplastic fibroblasts. Areas of caseation were observed and about them fragmented nuclei. When intact the epidermis usually presented no changes beyond a reduction in thickness.'' It should be added that giant cells are not infrequent. The process always begins in the perivascular lymphatics.

Squamous Syphilides

One other type of late syphilide remains to be described, the squamous, most generally known as the palmar or plantar syphilide. The thickness of the skin upon the palms and soles doubtless leads to this peculiar modification. The early lesions of syphilis, especially the papules, not infrequently affect these parts, showing as typical flattened scaling lesions, but the late lesions are different and eminently characteristic. These late lesions may appear as early as six months after the chancre, but usually develop at a much later period, often many years. When appearing early they are apt to be symmetrical but when occurring late they may be either unilateral or bilateral. These lesions are much rarer in the negro than in the white, just why it is difficult to say. These squamous syphilides may first appear in either one of two ways, as dull red macules or as slight reddish fissures in the lines. In either case the lesions usually speedily become covered by white, closely adherent scales, at least on the edges. In exceptional cases the primary lesion is a minute white spot, which spreads rather rapidly to form a typical lesion. In exceptional instances very small white centers are apparent in the lesions, these being due to the deposit of calcium salts, the syphilide cornée of the French authors. As the disease progresses the individual lesions spread slowly in a peripheral manner and occasionally clear up in the center. As a general rule the ultimate size of the patch is from one to two inches, but occasionally the whole palm may be involved. The edges are well defined and may show an elevated border. The lesions are of a dull red color and are covered by white scales, that sometimes become detached at one end so as to resemble splinters. Occasionally

the lesions may protrude to a considerable extent above the surface of the skin. Practically any portion of the palmar and

Fig. 72.—Early palmar syphilides are prone to develop in the lines.

Fig. 73.—After an injection of arsphenamine the condition depicted in the preceding figure developed into a ring-shaped lesion.

plantar surfaces may be affected, but the lesions but rarely appear upon or extend to the back of the hands or feet. Upon the sole they have a great tendency to spread up over the arch of

Fig. 74.—Usually in palmar syphilides the skin at the edges curls up and there are fine scales.

Fig. 75.—Palmar lesions may be more or less verrucose.

the foot. As a rule these lesions are remarkably persistent, but will usually heal under intensive treatment.

The diagnosis must be made from psoriasis and eczema, and is frequently very difficult. In psoriasis the presence of other le-

Fig. 76.—Palmar lesions may closely resemble eczema; in this instance there was some characteristic ulceration near the wrist.

Fig. 77.—In either palmar or plantar syphilides there may be small hard white spots, the syphilis cornée.

sions is essential to make a correct diagnosis. Fortunately these are practically always in evidence, for psoriasis does not occur in these locations alone. Eczema is almost always bilateral, and usually itches, especially after washing, but it should be remembered that a syphilitic lesion may become eczematous. Hence it

is often necessary to resort to the laboratory tests unless other evidences of syphilis are present.

The pathology of the disease does not differ materially from that of the other late cutaneous manifestations.

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CHAPTER VIII

CUTANEOUS COMPLICATIONS

The cutaneous complications of syphilis may be divided into dyschromias, atrophies, scars and keloids as the direct results of the pathologic processes in the skin. Subcutaneous calcification may occur deeper in the corium. As the result of irritating discharges we may see varying degrees of dermatitis or venereal warts. Telangiectases may develop in association with the infection. Keratoses appear at times. Cancer may appear in scar tissue. Arteritis may produce secondary skin changes. Eczema may occur also in connection with syphilis. And lastly some sarcoids and even erythema nodosum and scleroderma have been attributed to this infection.

Syphilitic Dyschromias

Sutton[1] has recently published a review of the various pigmentary changes. Either the secondary or tertiary lesions may leave pigmented or more rarely depigmented areas, the syphilitic leucoderma described in Chapter VI being one of the best known of the rarer forms. It is extremely common for papules to leave pigmented spots which may persist for many years. The same is true of either gummata or nodular lesions, and no further mention of them is necessary, except to point out their diagnostic importance; it is generally conceded that the presence of pigmented scars upon the upper portion of the shins is extremely suggestive of syphilis.

Atrophic Changes

A condition spoken of as atrophia maculosa luetica has been described by Alexander and Zenger,[2] Bohac,[3] Volk[4] and others. In this condition there are present either pigmented or somewhat depigmented, slightly depressed, atrophic spots that to some extent resemble old chicken pox scars. They are apparently due to a destruction of the elastic tissue.

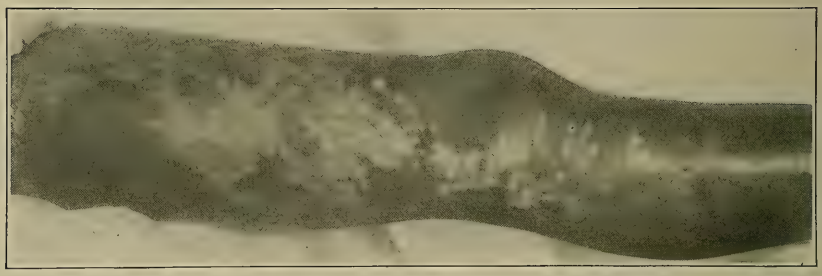

Fig. 78.—As a result of syphilis remarkable pigmentary changes may develop. These lesions are not always influenced rapidly by treatment.

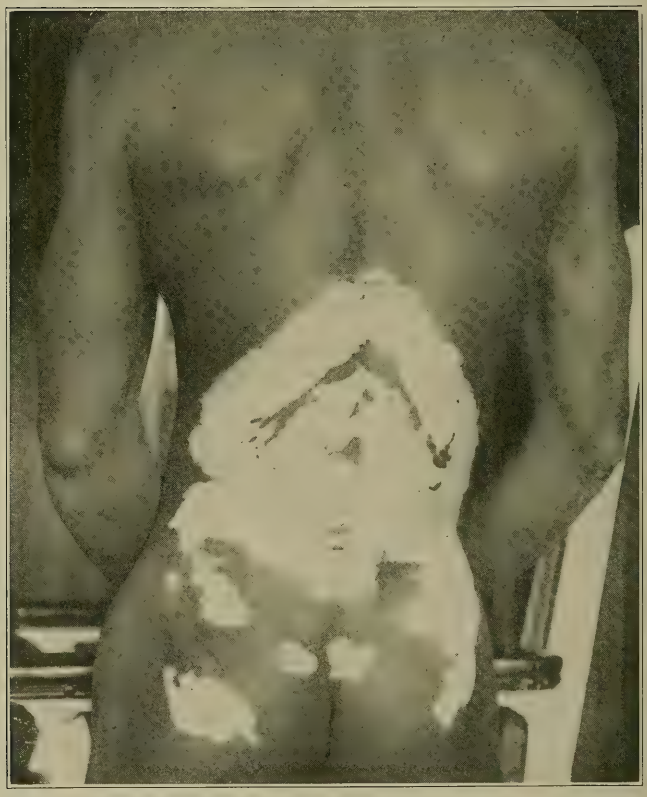

Fig. 79.—Marked depigmentation may follow syphilitic ulceration. (Collection of Dr. Richard L. Sutton.)

Scars

In exceptional instances resolving papular lesions may leave behind them true depressed scars. The pustular lesions, if of sufficient depth, do this with considerable regularity. All of the late cutaneous lesions are very prone to leave scars, often of great extent. As a rule these scars are of the atrophic variety.

Fig. 80.—It is unusual for scars to follow early papular syphilides, but occasionally this may take place.

However, at times keloids may arise in syphilitic scars. Dittrich[5] has reported a case where a keloid developed upon the site of nodular syphiloderm. Curiously enough I have but once seen such a case in the negro race, although several of my friends tell me that they have encountered a number.

Subcutaneous Calcification

Stradiotti[6] has put upon record a case where multiple calcified areas appeared in the subcutaneous tissues.

Telangiectasis

Stokes[7] has recently published a very complete paper upon the subject of telangiectasis associated with syphilis. While these cases are undoubtedly rare, still it is possible that many cases of telangiectasis of obscure origin may be due to syphilis. Women are more apt to be affected than are men, twenty-two females as against eleven males having been reported. Many of the cases show other evidences of cardiovascular involvement. As a rule the lesions first appear upon the extremities. The lesions may be macules, papules, puncta, bands, arborescences, gyrate figures, or simply mottlings. Either atrophy or changes in pigmentation may result. Histologically definite syphilitic changes are found in the blood vessels of the affected parts.

Dermatitis

It is not unusual for the discharge from an ulcerated gumma to cause a true dermatitis upon the part of the skin with which it comes in contact. I[8] have recorded an instance where this dermatitis became verrucose, and have since seen several others, less severe in type. Ordinarily the healing of the primary lesion will cause the speedy resolution of the secondary changes.

Venereal Warts

Ravogli[9] has recently reviewed the subject of venereal warts associated with moist syphilitic lesions, pointing out that they are caused by irritation and in no sense are to be regarded as of a true syphilitic nature.

Keratoses

While it is more or less generally recognized, as has been pointed out by Ealer,[10] that hypertrophic lesions of late syphilis may become hyperkeratotic, still it should always be remembered that a type of plantar or palmar keratosis exists, which resem-

bles the congenital type, but which is directly due to syphilis. Gaucher and Flurin[11] have reported an instance of this kind. These keratoses in all probability arise upon syphiloderms.

Fig. 81.—A vegetative dermatitis may follow upon the discharge from gummatous ulcerations.

Cancer

It is well known that cancer of the tongue frequently arises upon a lesion of syphilitic nature, either a leukoplakia or a fis-

sure. However cancer of the skin may arise either in an unhealed gumma or the scar resulting from an ulcerative syphiloderm. Such cases have been reported by Garibaldi,[12] Winfield,[13] Whitehouse,[14] Gottheil,[15] Heidingsfeld[16] and many others. These lesions are very apt to be of the spino-celled type and hence to metastasize quickly.

Syphilitic Arteritis

Syphilitic arteritis may produce changes of varying intensity in the overlying skin, varying from a simple inflammation to a loss of tissue. The parts supplied by the vessel obliterated may become gangrenous. All depends upon the size and number of the vessels involved, the collateral circulation and the intensity of the syphilitic process.

Eczema

I[17] have published four cases where an acute eczematous process flared up at the same time that the secondaries appeared. Since that time I have seen two more cases. The type of eczema may be either erythematous, vesicular or papular, but most often the second. No treponemata can be demonstrated in the lesions so it is probable that a diminished bodily resistance allows the eczema to develop. It is interesting to note that as a rule the eczema will not heal until antisyphilitic treatment is beginning to manifest its results.

Sarcoids

Pautrier[18] suggests that some cases of sarcoid are of syphilitic origin, since the patients show positive complement-fixation reactions, and the lesions heal under antisyphilitic treatment.

Erythema Nodosum

The true erythema nodosum is an infectious disease, due to a variety of the streptococcus, as Rosenow[19] has shown. However, there is a variety of syphilitic phlebitis that much resembles this affection. Cases have been described by Hoffmann.[20] There is also another form, in which there are subcutaneous gummata, first described by Mauriac, where the lesions usually appear upon the arms and legs, and which may markedly re-

semble erythema nodosum. This latter type has been fully discussed by Leviseur.[21]

Scleroderma

Whitehouse[22] has shown that many subjects of scleroderma give positive Wassermann reactions, but at the present time it is not generally believed that syphilis bears any etiologic relationship to the disease.

Raynaud's Disease

This subject will be discussed in the chapter dealing with syphilis of the circulatory organs.

Urticaria

The literature does not deal with syphilis as a basis for urticaria. However, my own experience in this line has been markedly different. In making routine examinations for factitious urticaria in the subjects of secondary syphilis I have been struck by the number of times that this has proved positive. In the negro race there can be no doubt but that chronic urticaria is frequently caused by syphilis, is cured by antisyphilitic treatment, and relapses as soon as such medication is stopped. In my clinic nearly one-third of the cases of chronic urticaria were definitely caused by lues.

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CHAPTER IX

LESIONS OF THE NAILS AND HAIR

Excellent accounts of syphilitic lesions of the nails may be found in the works of Heller,[1] Ormsby,[2] and Adamson and McDonagh.[3] It is generally conceded that there are three different types, first the chancre, second disease of the nail substance and last involvement of the surrounding tissues.

Chancres of the fingers are not uncommon as has already been stated. The presence of minute breaks in the skin around the nails gives a favorable place where the treponema may gain entrance. The common type of initial lesion is that which has already been described under the heading of extragenital chancre. However, there is another type to which White[4] has called attention, namely the wide margined one composed of an exuberant mass of granulation tissue springing from the nail fold. This may cause parallel ridges in the nail-plate, or even the loss of the nail.

Syphilis of the nail-plate is also called syphilonychia sicca, friable onychia, scabrities unguium syphilitica and onychia sicca syphilitica. Heller saw only three examples in over eight thousand cases of syphilis, and Rayer[5] and Bergh[6] also speak of its rarity. On the other hand Fournier[7] and Pringle[8] do not consider it so unusual. Nine types of lesion have been described.

1. There may be a brittle condition of the nails, so that the free ends tend to split and break, and as a result the nail border is splintered or serrated. All of the nails may be involved, but more especially those of the hands. There is probably no thickening or thinning of the nail, but simply a change in its quality so that it is more brittle.

2. In the dorsal surface of the nail there may be pits, sometimes arranged in a line from the root forwards. Batut[9] states that they begin as whitish points which can be dug out, and which leave roughened, black holes.

3. The whole nail may become dull, dry, thick, brittle and hence cracked at its free margin. Cazanave[10] states that in some instances there is a distinct line of demarcation between the diseased and sound parts. This is due to the fact that a diseased portion grows up behind the sound section, or that a healthy nail is again making its appearance behind the syphilitic portion.

4. Rarely there occurs a hard, wedged-shaped thickening of the distal end of the nail.

5. The nail may exfoliate without any subjective or objective symptoms.

Fig. 82.—In syphilis one or several nails may be affected. In the case pictured the affection was of many years' standing.

6. Heller[11] has recently published two cases which are sufficiently described by the title that he has given them, namely "Striae longitudinales medianae unguium syphiliticae."

7. It is well known that any disturbance of nutrition may cause a grooving of the nails. Whitfield has noted that this occurs in syphilis as well as in other diseases.

8. Vörner[12] has described black pigmented spots in the lunula, developing at the same time as a generalized secondary eruption.

9. Dr. H. R. Varney considers that "spoon nails," whose general characters are well shown in the illustrations are pathognomonic of syphilis. These changes must be rare, as I have looked for them for two years and have not seen a case.

Fig. 83.—Symmetrical saucered nails. Pathognomonic of syphilis. (Collection of Dr. H. R. Varney.)

Fig. 84.—Symmetrical saucered nails of syphilis. (Collection of Dr. H. R. Varney.)

Fig. 85.—Symmetrical saucered syphilitic nails, showing correction following treatment. (Collection of Dr. H. R. Varney.)

The second type of syphilitic nail is that in which the nail changes are secondary to local inflammatory changes in the surrounding tissues. Of this there are two types, where there is a papule or pustule on the nail-bed, and where there are syphilitic lesions surrounding the nail. Both of these eruptions are said to be more common than the type above described.

Heller calls the first "the isolated papule of the nail-bed." It may occur at any time during the exanthem. A small discoloration first appears under the nail, this becomes red and then yellow, and the overlying part of the nail gets thin and finally crumbles away, thus leaving a hole. It is practically always limited to one finger.

The last type of lesion is called paronychia, perionychia, paronychia desquamativa and syphilis ulcerosa unguium. Several nails or but one may be affected, and the thumb is the favorite site, possibly because more exposed to injury. On the foot the great toe is the usual location. The first symptom is swelling and redness of the tissues around the nail, usually with some pain. The inflammation may extend beneath the nail to the matrix and nail-bed. Either a crusted area or a deep ulcer may result, and the nail may be lost, sometimes permanently.

Syphilitic Alopecia

Klotz[13] has written an excellent article upon syphilitic alopecia. He calls attention to the fact that alopecia in syphilis is not as common as many of the textbooks would have us believe. We should always remember that every individual normally sheds his hair and that a slight daily loss is a perfectly natural and physiologic phenomena. However, in something under 10 per cent of all cases of early syphilis there is a characteristic loss of the hair in patches especially upon the back of the head. All of the hair in these spots does not fall, but from one-fourth to nine-tenths of it does drop. The size of the individual patch varies from one-half to two inches in diameter, and several patches may fuse. The general appearance has been described as "moth eaten," "mangy," "as if the hair had been carelessly cut with a dull pair of scissors," and as "alopecia in clearings." It is generally believed that the toxins of the treponemata are

Fig. 86.—The alopecia occurring during early syphilis is a patchy one, usually not so severe as in this instance.

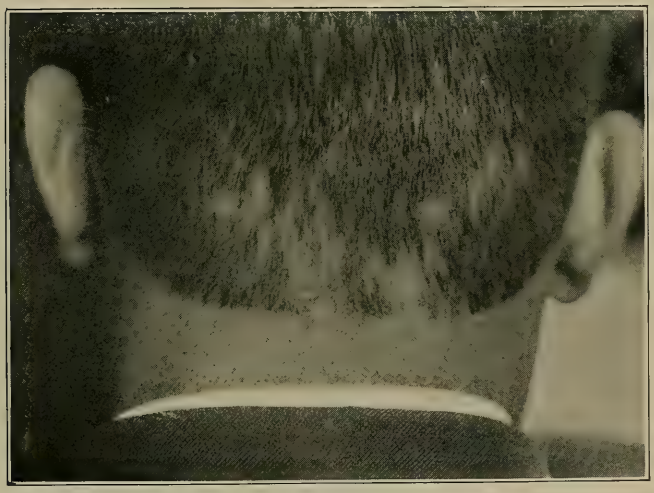

Fig. 87.—Syphilitic alopecia usually has a "moth-eaten" appearance. (Collection of Dr. Richard L. Sutton.)

responsible for this fall. In exceptional cases as White[14] brought out in the discussion of Klotz's paper complete and permanent baldness may result. This type of the disease is most common upon the scalp but may extend to the eyebrows, and even to the axillæ and genital regions. It is also probable

Fig. 88.—The eyebrows may be affected in early syphilis. (Collection of Dr. Richard L. Sutton.)

that in a severe case of syphilis there may be a general non-localized loss of the hair of the scalp just as occurs in association with other infectious diseases, and lastly there may be a syphilitic exanthem upon the scalp, and the hair fall at the site of the syphilides.

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CHAPTER X

AFFECTIONS OF THE MOUTH AND THROAT

In connection with the subject of syphilitic diseases of the mouth attention should be called to the excellent atlas of Zinsser's,[1] which portrays both the syphilitic lesions and those diseases which may simulate them.

The subject of chancre of the mouth has already been covered in the chapter dealing with the primary stage of syphilis, so this chapter will begin with an account of the secondary manifestations. These lesions are a part of the superficial widespread involvement that is the result of the septicemia that forms the pathologic basis for the early stage. At the same time it should always be remembered that the mucous membrane manifestations are prone to linger longer than are the cutaneous lesions and that they are often more resistant to mercurial treatment.

At the time of the appearance of the generalized eruption there may appear upon the mucous membranes simple erythematous spots, which may be either large or small and either transient or of long duration. These lesions give rise to no subjective disturbances and are frequently overlooked.

A better known type of erythema is the one that so frequently involves the isthmus of the fauces. This often has a very sharp line of demarcation, and is seen in a large percentage of all cases of secondary syphilis. On the other hand a similar condition is frequently found in a simple pharyngitis, so too much stress must not be laid upon it.

The most frequent and characteristic type of syphilis of the mouth is the mucous patch, sometimes called the erosive syphilide. This is round or more frequently oval, and practically never over two centimeters in diameter, and simply represents a syphilitic papule that has become transformed by its environment of heat, moisture and pressure. These mucous patches are most common on the inner surfaces of the lips, especially at the angles of the mouth, but are also found upon the pillars

of the fauces, the tonsils, the tongue, the buccal mucosa and even upon the pharynx. The surface of these patches is usually covered by a gray shining membrane that when detached reveals a superficial ulcer beneath. The lesions are sharply circumscribed and there is usually no inflammatory areola surrounding them.

Fig. 89.—Annular lesions may occur upon the mucous membranes as well as upon the skin

Fig. 90.—Mucous patches are the typical mucous membrane lesions.

They may become raised and hypertrophied due to the epithelium increasing in thickness, and then appear as rough, granular, even almost frambesiform lesions that often arise abruptly from normal mucous surfaces; they may be surrounded by a considerable areola of inflammation.

In some instances these mucous patches may undergo ulceration, either superficial or deep. This ulceration is frequently due to lack of treatment, and frequently due to various types of external irritation, as sharp teeth, excessive smoking, etc. The ulcers are usually surrounded by a considerable amount of inflammation.

Still another type of lesion is the opaline plaque, which Ormsby[2] considers may arise totally independently of mucous patches. These plaques are most apt to arise upon the dorsal surface of the tongue, but may also occur in the angles of the mouth and upon the buccal mucosa. They are flat, smooth,

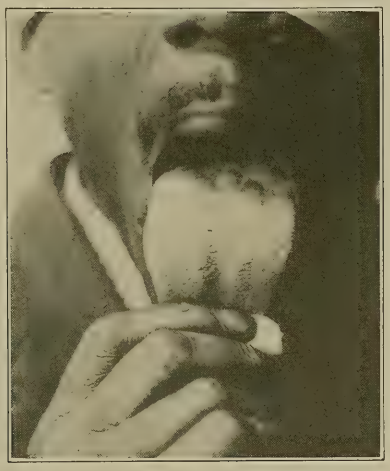

Fig. 91.—Papules may occur upon the tongue as well as upon the skin.

and whitish blue in color, firm and at times slightly indurated to the touch. Smoking probably plays an important part in their development. They are covered with thickened epidermis and are probably leucoplaktic in character.

In addition to the lesions already described, true papules may appear upon the dorsal surface of the tongue, and macular or annular lesions upon the lips. An interesting type of lesions is the large annular lesion of the roof of the mouth. In the negro this is by no means infrequent, and usually appears as a spreading circular or serpiginous eruption, the edges of which only are visible, and they are composed of erythematous lines,

which may or may not be covered by a gray necrotic membrane, similar to that covering typical mucous patches.

In the course of malignant syphilis severe ulcerations of the mouth and throat are usually found at an early date.

The diagnosis of secondary syphilis of the mouth is not always an easy matter, for there are a number of conditions that must be ruled out. It is well to point out that the mouth swarms with treponemata of various kinds, hence too much stress should not be placed upon examination with the dark-field illuminator. The presence of a positive Wassermann reaction is of course of great value, always remembering that a patient with an old history of syphilis may very well have some other condition as well. The following conditions must be differentiated:

Injuries to the frenum linguæ are frequently seen in children and occasionally in adults, hence ulcers near it must not always be diagnosed as syphilitic. Any spell of coughing or choking or marked protrusion of the tongue may cause a traumatic ulcer to form here.

Patches of any kind that have been touched with silver nitrate may markedly resemble mucous patches. Ulcers or scar tissue may follow the biting of the tongue, lips or buccal mucosa.

The clinical manifestations of mercurial stomatitis are usually very characteristic, but inasmuch as mercury is usually taken by syphilitic patients, and inasmuch as mercury may cause papules and ulcerations, the diagnosis at times may puzzle the wisest of us. As a general rule the typical mercurial stomatitis with its diffuse redness and swelling of the mucous membranes, salivation, the pus covered ulcerations upon the gums, swollen tongue, ulcers upon the cheeks produced by the teeth, and the marked fetid odor present a picture which is easy to recognize.

Just as there are drug eruptions upon the skin, so may there be within the mouth. The use of potassium iodide, phenacetin, antipyrin and the other coal tar derivatives produces eruptions in the mouth that may at times simulate syphilis. The fact that there is usually an itching eruption upon the body that has appeared at the same time as the oral lesions would cause one to suspect a drug rash, and if upon taking the history it be found to have followed the ingestion of drugs the diagnosis becomes

more probable. The eruption should disappear within a few days after the use of the medicine is discontinued.

The lesions of lichen planus upon the oral mucosa may simulate a syphilitic eruption, but the finding of the characteristic eruption upon the other portions of the body will enable the physician to make the correct diagnosis.

Erythema multiforme at times produces a superficial ulceration, especially upon the tip of the tongue and lips; the diagnosis is best made by lesions upon other portions of the body.

The lesions of aphthous stomatitis are especially apt to be mistaken for mucous patches. In most cases it is not difficult to make a proper differential diagnosis, for the lesions of aphthous stomatitis appear suddenly, either singly or in groups, are painful, and are always surrounded by a marked inflammatory areola. At first the central portion of the lesion is covered by a yellowish exudate that later turns gray. These lesions rarely last more than four or five days.

The transitory benign plaques of the tongue should not cause any trouble, inasmuch as they vary much in size and shape from day to day, a thing that a secondary syphilitic eruption never does. If seen but once, they may resemble annular syphilides, but the history should then save the day.

Late Lesions

Syphilitic lesions of the mouth and throat during the late stage of syphilis are very common, and may assume many forms. The lips, tongue, hard and soft palate, the tonsils, the pharynx, in fact any structure within the mouth can be attacked. The tertiary lesions are usually characterized by the destruction of tissue due to gummous growths. All are analogous to the growths in the skin and other organs. Small or large nodules may develop upon any portion of the oral mucosa; these may either break down to form more or less superficial ulcers, or may become sclerosed and form flat, reticulated cicatrices. More often, however, the gummata commence in the submucous tissues and as a result deep ulcers develop. In general the syphilitic neoplasms of the mouth have no special tendency to spread, yet those of the lips, tongue and particularly those of the soft palate

and fauces, may become large tumors, which upon breaking down cause very large ulcers. When this occurs the ulcers have irregular or arched borders, and often undermine the mucous membranes. The floor of the ulcer is uneven and bleeds easily, and is covered with either pus or a serous exudate. As a rule syphilitic lesions do not cause any great amount of pain. These ulcers are especially common about the soft palate and fauces, and frequently cause very extensive destruction of tissue within a short time. It is not uncommon to see the uvula and a large portion of the soft palate totally gone. Associated with such lesions there is always a marked erythema of much of the oral

Fig. 92.—Gummata of the tongue may be solitary and may resemble cancer. (Collection of Dr. Richard L. Sutton.)

Fig. 93.—A gumma of the tongue is not especially uncommon. (Collection of Dr. Richard L. Sutton.)

mucosa. Similar lesions upon the walls of the pharynx may occur, either independently or in connection with syphilitic lesions in other parts of the mouth. At times death may ensue from the rupture of a large blood vessel.

The gummous processes in the lips and tongue usually do not run so violent a course, for the tissues are denser and more resistant, so the lesions are usually smaller and more sharply circumscribed, and resemble those found upon the skin to a more marked degree.

It is not rare for gummata to originate from the underlying bone or periosteum. This is most apt to occur in the hard pal-

ate, and always results in the local necrosis of bone, with the frequent formation of a fistula through the roof of the mouth. At this point it is well to call attention to the great diagnostic importance of such perforations of either the hard or the soft palates, for a fistula in either is practically pathognomonic of syphilis. It is usual for such a lesion to make considerable headway before the patient is aware that there is any trouble whatever, and frequently the first indication is the sloughing out of pieces of bone. However, the first evidence is, of course,

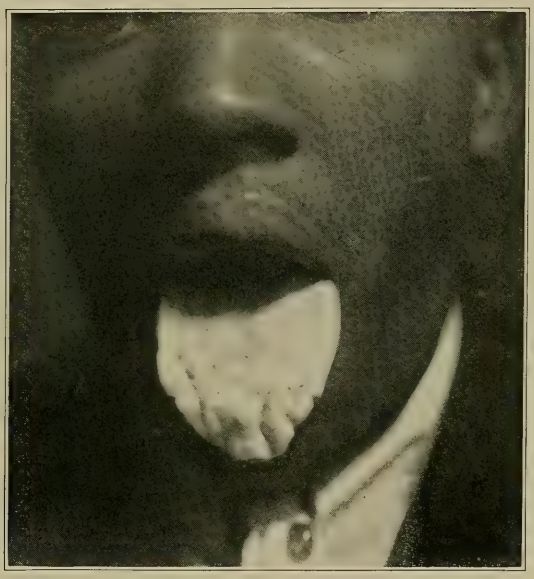

Fig. 94.—Interstitial gummous glossitis is fairly common and gives rise to deep fissures.

a soft swelling of the mucous membrane over the affected area, the center of which soon breaks down. Very extensive destruction may take place unless treatment is energetically carried out; the mouth and nasal cavity may become one. In all cases of ulcers of the mouth a probe should be used to determine whether there be any underlying necrosed bone.

The healing of gummous ulcers in soft tissue always results in scar tissue formation, and this is apt to be in the form of radiating cicatrices, which distort the noninvolved adjacent tissues. Juxtaimposed ulcerating surfaces often become united; hence it

is not uncommon to find the uvula and even more of the soft palate united to the posterior wall, while respiration may be carried on through a perforation of the palate. Very small perforations of either the hard or soft palate may close spontaneously, but the large ones remain open unless operated upon.

In addition to the nodular and gummous lesions there is still a third type of lesion, the sclerotic one, that to some extent resembles the diffuse gummata of the skin and the interstitial scleroses that occur in the viscera. This occasionally affects the lips, which become thickened, infiltrated and fibrous, and which may be covered by superficial ulcerations. They usually have a more or less snout-like appearance and are sometimes called syphilitic leontiasis.

Such interstitial lesions of the tongue are frequent. Symmers[3] has made an especial study of this condition, and inasmuch as it is of great importance from a diagnostic standpoint I shall quote rather freely from his article.

"In this country N. B. Potter appears to have been the only one to attempt to determine the clinical value of smooth atrophy of the tongue. This observer examined the tongue in nearly four hundred individuals, and arrived at the conclusion that when the root is normal it is probably of considerable value in excluding syphilis, that typical smooth atrophy in an individual below fifty years of age points to syphilis, and that a moderate or slightly marked degree of atrophy is of little value in respect to syphilis.

"Before proceeding further, it might, perhaps, be of interest to recall that, in normal conditions, the root of the tongue presents on either side of the median raphe between the circumvallate papillæ in front and the epiglottis behind, about a dozen nodular elevations, each of which is rounded or oval in outline and about 2 mm. or 3 mm. in diameter, and presents at its center a small crypt-like depression. These nodules lie in the connective tissue immediately beneath the stratified squamous epithelial covering of the tongue, and correspond, histologically, with lymphoid follicles in which germinal centers are practically always discernible. Still deeper in the substance of the tongue numbers of mucous glands come into view, but seldom if ever do they approach sufficiently close to the surface to be felt by

the finger or to become apparent to the unaided eye. Beneath these structures striated muscle bundles are found. Running between them and supporting these several elements are delicate connective-tissue trabeculæ.

"It appears that at the base of the tongue the lymphoid structures not only share in the hyperplasia met with in these tissues as a whole in secondary syphilis, but that the follicles become enlarged in a variety of other conditions. * * *

"Examined by the naked eye the base of the tongue on either side of the median line in such circumstances exhibits from twelve to twenty-five or more pale, discrete, lymphoid nodules, varying in diameter from 3 mm. to 7 mm., and often so closely aggregated that the intervening epithelial covering is entirely obscured. * * *

"In the condition to which Virchow gave the name 'smooth atrophy' the base of the tongue presents characteristic changes.

"In the least advanced cases the base of the tongue is pale, flattened, relatively smooth, and firmer than normal, and the lymphoid follicles are few and small. In some instances they lie at the periphery of the tongue; in others they may be seen as pinhead-sized or slightly larger nodules scattered at remote intervals beneath the epithelial layer. In cases further advanced the lymphoid follicles are invisible to the naked eye, and the surface of the base of the tongue is pale, smooth, markedly flattened, and very firm. In a considerable proportion of these advanced cases the epiglottis is pulled forward or to one side. * * * On section through the tongue it is found that immediately beneath the epithelial layer the tissues for about 2 mm. or 3 mm. are pale, often hyaline in appearance."

Microscopic examination shows that the epithelium is thinned, and that the connective tissue of the submucosa has been transformed into a thick hyaline mass which is irregularly vascularized and encloses collections of lymphoid cells. The germinal centers are absent.

Symmers states that there is a second type of atrophy of the base of the tongue in which a number of isolated scars appear, producing smooth indurated depressions in the surface of the organ. Both types are, of course, due to a replacement fibrosis. He concludes that this smooth atrophy is invariably the result

of syphilis, and that it is of great value in the diagnosis of late syphilis.

In a more recent article Symmers[4] states:

"On the other hand one often encounters simple smoothness and flattening of the base of the tongue in elderly or cachectic subjects in whom there is no reason to suspect syphilis, but in these individuals the essential feature of Virchow's smooth atrophy is lacking, namely the induration due to connective tissue replacement. Therefore, in approaching the diagnosis, both

Fig. 95.—Perforation of the palate is almost pathognomonic of syphilis. (Collection of Drs. Fordyce and MacKee.)

from the clinical and anatomic point of view, the finger should be trained to appreciate the degree of resistance offered by the base of the tongue, and the sense of sight used only as an adjunct to that of touch.

"The incidence of indurative atrophy of the base of the tongue has not been definitely determined. For example, among 632 necropsies performed at the New York Hospital by Dr. Elser and myself, acquired syphilis was determined in 75 instances, and of this number 64, or, 85 per cent, presented the classical signs of indurative atrophy of the base of the tongue."

No examination for syphilis in the late stages is complete without an investigation as to the presence of this sign.

In addition to atrophy of the base of the tongue it is not rare to find an interstitial syphilis of the anterior portions of the tongue as well. The tongue is rigid and stiff, radiating furrows appear, and papillæ are usually lacking over the affected area. The surface may be thrown into lobes, the so-called cobblestone tongue. More commonly where the teeth come in contact with the edges there may be found fairly deep furrows, which are often covered with leucoplaktic spots, and which may even go on to ulceration. The edges of the tongue then have a distinctly serrated appearance. It should always be remembered that such lesions are very prone to undergo carcinomatous degeneration.

The late lesions of syphilis may be simulated by both cancer and tuberculosis. As a general rule in tuberculous lesions of the mucous membranes there is a characteristic white color to the mucosa surrounding the lesion. In still other instances miliary tubercles can be found in the mucous membranes. The growth of these tuberculous lesions is usually very much slower than that of the syphilitic lesions. Other evidences of either syphilis or of tuberculosis are of extreme value in making a positive diagnosis. Tuberculosis does not start primarily in the bones, but may later invade them. Tuberculous lesions are usually much more painful than are the specific manifestations.

Cancer grows much more slowly than does syphilis, it is more apt to affect those past middle life, and is usually associated with considerable pain. There is usually a hard, cartilaginous edge. Neighboring glands are sure to be involved at some time, although rarely before six months.

Leucoplakia

The question is still undecided as to whether or not leucoplakia is always of syphilitic origin. At the present time most observers believe that the majority of cases of leucoplakia are directly due to syphilis, but that a certain percentage of cases are not. Excessive smoking is undoubtedly a factor in the development of this disease. Another factor that should never be disregarded is irritation produced by rough teeth. McDonagh[5] goes so far as to say that leucoplakia is simply the effort on the part of the

tongue to produce a covering that will resist irritation, and that it can usually be cured by removing the irritating cause. However, I have seen a number of instances where this did not suffice to remove the lesions characteristic of the disorder.

The parts usually attacked are the dorsal and lateral surfaces of the tongue and the buccal mucosa at the tooth line. When well-developed, white, thickened plaques that soon become confluent can be seen. Later there is some fissuring. The tongue is very sensitive to tobacco smoke or to hot or cold food or

Fig. 96.—While irritants play an important part in causing leucoplakia, still syphilis is frequently a most important predisposing factor. (Collection of Drs. Fordyce and MacKee.)

drinks. A large percentage of these lesions eventually become carcinomatous. Histologically there is both parakeratosis and acanthosis, with an atrophy of the papillæ. There is round-celled infiltration in the submucous tissue.

If the disease is seen early all irritating substances should be prohibited; this means that smoking must be forbidden, and that no highly spiced foods are to be eaten. Neither should very hot nor very cold substances be taken. The teeth should be carefully gone over. If after three months of such a regime there is not re-

covery, the patches should be removed with the cautery. Under no circumstances should superficial caustics be applied; they are simply irritants and do more harm than good.

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CHAPTER XI

AFFECTIONS OF THE RESPIRATORY TRACT

An idea as to the frequency of syphilis of the respiratory tract may be obtained from the autopsy figures of Symmers.[1] In 314 cases of late syphilis he found lesions of these organs in thirty-five, or 10.5 per cent. The larynx was involved twelve times, the lungs twelve times, the pleura twice, the trachea four times, and the nose in five cases.

Syphilis of the Nose

Mackenzie[2] gives an entertaining sketch of the ancient history of syphilitic affections of the nose, that well rewards perusal.

Chancres of the nose are distinctly uncommon; Thomson[3] states that they form about 3 per cent of all extragenital chancres, but this is undoubtedly a rather high estimate. Cases have been reported by Lenoble,[4] Garel,[5] Tissier,[6] Loeb[7] and Freudenthal.[8] Initial scleroses are most apt to occur in the vascular areas, and are usually due to picking the nose. The lesion has the usual characteristics of chancre, but is rarely diagnosed before the secondaries appear. Certainly if the preauricular gland should early become enlarged chancre should at least be suspected more promptly. Malignancy has usually been feared, notwithstanding the rapid development of the growth.

Early syphilis of the nose is stated to be common in the congenital type of syphilis, but to be rare in the acquired type. However, Lieven[9] has described both an erythema and papules. When these occur upon the nasal mucosa they give rise to symptoms suggestive of a coryza, and upon examination the turbinates will usually be found congested. Mucous patches have been described as occurring on the anterior end of the septum and upon the inferior turbinate.

Late syphilis of the nose is not especially uncommon: Willijk[10] states that it occurs in 2.8 per cent of syphilitics coming to autopsy. These lesions occur at the same time that other late

lesions become manifest. Gummata may start in either the submucous tissue or in the periosteum or perichondrium. The bony septum is a frequent site, but any portion may be attacked. The course is very similar to that described in the section dealing with gummata of the mouth. If the lesions start in the bone there is rapid destruction of this substance, and there may be great resultant deformity, for the bridge of the nose not infrequently becomes depressed to a great degree, due to the lack of a bony support. Frequently there is considerable pain, that may be referred to the head. Tenderness over the bridge of the nose on pressure is stated to be a valuable diagnostic sign. If the gumma is seen before it has ulcerated, it will appear as a firm red swelling that does not shrink upon the application of cocaine. As a matter of fact, it is unusual to see a case before ulceration has occurred, and then an ulcer is evident, often with some dead bone in it. In some instances the gumma may perforate externally and then a sinus will be formed from the nasal cavity to the exterior of the skin. There is usually a very foul odor associated with extensive syphilitic ulcerations of the nose.

As a result of syphilitic disease an atrophic rhinitis (syphilitic ozena) may result. Owing to the destruction of ciliated epithelium and erectile tissue, the dry surfaces become coated with crusts. Tertiary syphilis must be differentiated from cancer, and this usually is not difficult, for a cancerous growth is practically always of slower development.

Syphilis of the Larynx

On the subject of syphilis of the larynx three of the most valuable articles are those by Beck,[11] Demetriade[12] and Thomson.[13] I have drawn largely upon the short article by the first named. Chancre of the larynx is extremely rare. Beck states that primary sores upon the epiglottis have been reported by Mackenzie, Moure, Pryat, Krishaber and Castex, and that Sarpemone has seen one in the larynx proper. On the other hand secondary syphilis of the larynx is not rare. All clinicians know that it is not uncommon to have a patient with secondary syphilitic lesions show a marked huskiness of the voice upon speaking, a huskiness that has every evidence of being laryngeal in origin. The secondary lesion may be a purely catarrhal one, in

which there are macules upon the mucous membranes, although at times there may be an associated edema as described by Lacroix.[14] Papules have also been described, and occasionally condylomata, the latter usually being situated upon the edges of the vocal cords. In the late stages condylomata may be found, as reported by Aronson;[15] there may be a diffuse gummous infiltration, or a nodular lesion or even a true ulcerating gumma. Lastly there is a perichondritis that usually starts in the arytenoid, and this is apt to be accompanied by suppuration. In the majority of instances it is necessary to rule out tuberculosis and the neoplasms and this can often be done by laryngeal examination, but in many instances laboratory aid must be called in as well. Although gummous new growths are comparatively rare it is certain that in cases of suspected cancer it is necessary to exclude syphilis. The end results of gummata of the larynx are considerable destruction of tissue and replacement by fibrous tissue, so that much deformity may result if treatment is not begun early. In some cases breathing may be rendered very difficult, and operative interference demanded.

Syphilis of the Trachea

It is stated by a number of authors that the secondary eruption of syphilis at times occurs upon the mucosa of the trachea. However, far and away the most important lesion is the diffuse gummous infiltration that leads to stenosis. This subject has been well covered by E. H. Reede,[16] and the following is derived from his article. Cayol[17] in 1810 first recognized that syphilis could cause lesions in the trachea without lung or laryngeal involvement. The first clinical observations on a case of this kind were probably those of Worthington[18] in 1842. Gerhardt[19] has reported five cases of his own in addition to collecting seventeen others from the literature. Vierling[20] tabulated the important features of forty-six cases. In 1903 Connor[21] added eighty-two cases to those already reported by Vierling. Gerhardt divides the course of the disease into three stages: that of irritation, that of stenosis, and that of suffocation. The first corresponds to the stage of gummous infiltration, the second to that of organized and permanent contractures, and the final stage

to a further narrowing of the lumen. In the first stage the symptoms in one case that I saw with Reede were a dry and paroxysmal cough of a distinctly brassy character and shortness of breath. The expectoration was scanty and mixed with blood. A well-marked inspiratory stridor was present over the sternum. In the second stage the symptoms are dyspnea of an inspiratory type, an inspiratory retraction of the soft tissues near the attachment of the diaphragm and in the region of the clavicle, and an inspiratory stridor which is the most important sign of all. Suffocative attacks are symptoms of the final period. The diagnosis can be made positively and directly by means of the bronchoscope. Differential diagnosis must be made from asthma, tracheal stenosis due to constriction from without or to cancer. X-ray examination will rule out stenosis from external causes, and also the presence of foreign bodies within the trachea. Laboratory tests positive for syphilis are also of value. The pathological condition is that of replacement of diffuse gummous infiltration with scar tissue. The prognosis is always serious unless the cases are diagnosed before the infiltration is fully established. However, when there are manifestations of the second stage arsphenamine may greatly aid the condition, as in the case that Reede and I saw together. The mortality of the reported cases is over seventy-five per cent. Tracheotomy is not of much value in the treatment because the lesions are usually situated at the bifurcation of the bronchi, and the bronchi themselves are frequently involved.

Syphilis of the Bronchi

Syphilis of the bronchi is very apt to occur in association with syphilis of the trachea, and like syphilis of that organ is unusual. As already indicated a favorite site for late involvement of the diffuse type is at the bifurcation of the trachea; hence both trachea and one or both main bronchi are frequently involved in the same lesion. However, one or both main bronchi or some of their ramifications may be independently invaded. Connor states that there may be four types of lesions, gummata, ulcers, endobronchial fibrous tissue, and peribronchitis. Lesions of the bronchi are frequently associated with those of the larynx, lungs,

or mouth, nose, and throat. As stenosis is the usual result of such lesions, it is the usual rule to find the same group of symptoms that has already been described under the heading of syphilis of the trachea, namely, cough, inspiratory dyspnea and stridor. There may be cough, pain, and alterations in the voice.

As a complication of syphilitic lesions of the bronchi bronchiectasis may supervene. Osler[22] states: "Included in this term are all cavity formations in the lungs consequent upon syphilis of the bronchi. It is not rare in association with syphilis of the lungs, resulting either from breaking down of lung substance about the bronchi or from bronchial constriction and dilatation." He states that there are three types, one where the lower lobes are the seat of an interstitial pneumonia with an associated general dilatation of the bronchi of the part. "The whole of the lobe is usually affected; the pleura is adherent and is considerably thickened. The lobe is large and firm. On section there are bronchiectatic cavities separated by a grayish fleshy tissue without that firmness usually seen in interstitial tissue." There is a second form in which there may be a single large cavity with loss of substance in an upper lobe. The third type is the one that follows on constriction of one of the larger bronchi. The symptoms of bronchiectasis are fever, wasting and loss of strength, cough which is usually more severe in the morning, abundant expectoration of a purulent character, occasional hemoptysis and frequently marked dyspnea. The physical signs are those of bronchiectasis, consisting chiefly of dullness and cavity signs. Clubbing of the fingers may be present. The diagnosis must be made from pulmonary tuberculosis, bronchiectasis due to other causes, and other types of syphilis of the lungs or bronchi.

Syphilis of the Lungs

Syphilis affections of the lungs still remain a source of much dispute among both clinicians and pathologists. The teaching a generation ago was that syphilis undoubtedly predisposed towards consumption. Virchow[23] was one of the first to accurately describe this condition. Wagner,[24] Calomiatti,[25] Carlier,[26] Hiller,[27] Heller,[28] Flockman,[29] Herxheimer,[30] Brandenberg,[31] Hutchinson,[32] Milne,[33] Culver[34] and many others have reported cases

of this condition. One of the best systematic studies of pulmonary syphilis that I have been able to find is that by Osler.[35] It is worthy of note that the clinician considers the condition to be fairly common, while the pathologist still considers it very rare. J. K. Fowler,[36] after studying specimens in all of the London hospitals, was able to collect but ten positive and two probable cases. Out of twenty-five hundred autopsies at the Johns Hopkins Hospital there were found twelve instances of this condition. In six thousand cases of syphilis taken from the records at the Hospital at Copenhagen there were but two of pulmonary lues.

Pathologically several types may occur. Gummata either single or multiple may occur in the lung, usually in one of the fibrous septa and most often near the hilus of the lung, although occasionally near the pleura. These gummata may be very small or they may be as large as a hen's egg. Their course is that of gummata in general, that is late caseation, or even more frequently fibroid degeneration. A second type is where an interstitial gummous formation occurs, much as in the case of the skin or tongue, and where the miliary gummata are replaced by fibrous tissue, often in thick bands and usually radiating outward from the hilus of the lungs. Lastly there may be a mixed form, consisting of fibrous tissue formation, gummous changes and pneumonic affections, as well as cavity formation and often bronchiectasis.

Clinically there are four types. The latent, the subject of a recent paper by Landis and Lewis,[37] may be commoner than is usually thought. The patients may be well-nourished and show no clinical signs of pulmonary trouble or they may show indications that are diagnosed as pulmonary tuberculosis in an early form. Usually there is some loss of weight, some cough with expectoration, and occasionally night sweats and some fever. I have seen two such cases: in one instance the patient entered a dispensary for tuberculosis because of supposed early lesions at both apices. Examination revealed a gumma upon the leg, and she gave a definite history of a chancre of the lip four years before. No tubercle bacilli could be found in her sputum, neither was there any change in her pulse rate or in her temperature curve. The tuberculin reaction was negative. Under antisyphi-

litic treatment all physical signs in the lungs disappeared within a month, and she remained well for at least two years. In the second case a woman of thirty-six came to me because of a palmar syphilide. History revealed the fact that she was considered to be tuberculous, because she had suffered from at least twenty-five pulmonary hemorrhages, and that there were some slight signs of a thickened pleura at the right base. Just before receiving an injection of arsphenamine she had a hemorrhage, and several more followed in the course of the next month. She was then put upon arsphenamine, followed by intramuscular injections of mercury, and the hand cleared up and there has been no further pulmonary trouble. It is worthy of note that in this case also there was no disturbance of either the pulse rate or of the temperature. Of course it is well known that many of these cases do unquestionably show varying types of fever.

A second type of syphilis is where there is definite local cavity formation, due to the ulceration of a gumma into the bronchi. These cases usually resemble tuberculosis very closely.

The third group consists of the so-called "syphilitic phthisis" cases. In this group there is a progressive fibrocaseous course that can not clinically be distinguished from tuberculosis. Cases have been reported by Fowler,[38] Osler[39] and Buchanan.[40]

Still a fourth type is the fibroid one, which is clinically indistinguishable from fibrosis due to any cause. Cases have been reported by Osler[41] and E. C. Perry.[42]

Fowler lays down the following postulates which must be fulfilled before a certain diagnosis of pulmonary syphilis can be made:

(I) The cases must be complete, that is, the symptoms observed during life must be considered in connection with the lesions discovered on postmortem examination.

(II) The evidence of syphilitic infection must be undoubted.

(III) Repeated examinations of the sputum must have been made, and tubercle bacilli have been invariably absent, and the absence of tubercle in the lungs as the cause of the lesions must be proved by postmortem examination.

(IV) Syphilitic lesions about the nature of which there can be no doubt must be found in other organs.

However, in order to cure our patients who are suffering from

pulmonary syphilis, we must make at least a tentative diagnosis long before the postmortem period. I am firmly convinced that every case of chronic lung trouble should have a Wassermann performed, and that if it be found positive, or if there be any evidences whatever of lues from either the history or the physical examination, pulmonary syphilis should be ruled out if possible. It is difficult to cure cases of pulmonary tuberculosis but relatively easy to improve instances of pulmonary syphilis. If there be definite evidences of syphilis from either the laboratory or the clinical side and if tubercle bacilli are absent, the patient should receive the benefit of the therapeutic test, namely, arsphenamine. So far in my experience, x-ray examination has not proved especially helpful in distinguishing pulmonary tuberculosis from pulmonary syphilis.

Syphilis of the Pleura

There is considerable discussion as to the occurrence of syphilis of the pleura. It undoubtedly does occur in association with lung syphilis, but as a primary disease it must be extremely rare, although probably not unknown, inasmuch as syphilis affects practically every other organ of the body. Vasoni[43] claims that to date there is no sufficient evidence of a pure form of syphilitic pleurisy. To make an unquestionable diagnosis he states that the exudate should show a positive Wassermann, while the blood Wassermann is negative. Roger[44] has reported two instances of pleurisy with effusion in which the findings of tuberculosis were consistently negative and which very promptly cleared up under antisyphilitic treatment. Barker[45] says that he has met with one case of widespread gummous infiltration secondary to lung syphilis which cleared up very rapidly under arsphenamine. Schlesinger[46] has published the most comprehensive review of the subject.

Syphilis of the Mediastinum

Creyx[47] believes that syphilis should be excluded in all cases of mediastinitis either in children or adults. In the former, syphilitic glands may give rise to trouble and in the latter there

may be syphilitic lesions associated with the esophagus, trachea, or aorta.

Giffin of the Mayo Clinic has reported five cases, and Stokes, of the same institution, tells me that he has seen a number of cases in which cyanosis in a supine position was a very pronounced symptom. Corrae[49] and Renault[50] have published theses on this subject. The symptoms of mediastinal inflammation have been well summarized by Howard.[51]

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CHAPTER XII

SYPHILIS OF THE DIGESTIVE TRACT

Syphilis of the mouth has already been considered in a special chapter devoted to that subject alone.

Syphilis of the Salivary Glands

Haslund[1] has recently reviewed the literature upon syphilis of the salivary glands in addition to reporting a case of his own. Gerber[2] has written the most complete monograph upon the subject in existence. These two articles give a complete bibliography. It is generally agreed that in the course of acute secondary syphilis the parotid and more rarely the submaxillary and even the sublingual glands may swell so as to simulate mumps. The condition, however, is extremely rare. It is due to an acute parotitis, that usually subsides rather promptly upon antisyphilitic treatment. According to Haslund, it is usual for the overlying preauricular lymph gland to be involved as well.

In tertiary syphilis the swelling usually affects one gland only, while in secondary syphilis the affection is almost invariably bilateral, and usually develops slowly and painlessly. As a rule the swelling is adherent to all of the surrounding tissues and hence is usually diagnosed as a malignant tumor. While the parotid is the gland usually affected, any of the other salivary glands may be the site of election. There may or may not be manifest luetic lesions in other organs. Microscopically the lesions are typically gummous.

Syphilis of the Esophagus

The subject of syphilis of the esophagus has recently been thoroughly reviewed by Wile,[3] and the following account is derived entirely from his article.

Compared with the frequency of syphilitic affections of the mouth and pharynx, and for that matter of the rectum as well, specific lesions of the esophagus are very rare. Syphilis of the

esophagus was first mentioned by Severinus[4] in the middle of the eighteenth century. Gastou, who wrote the chapter on syphilis of the digestive tract in Fournier's[5] great book, was able to collect but forty cases of esophageal lues, and ten of these were doubtful. One of the best accounts of the pathologic anatomy of the affection was by Virchow.[6] In 1883 Lublinski[7] reported two cases of his own in addition to giving an extensive review of the literature, and in the following year Jullien[8] published a monograph on the subject. The American literature is almost completely lacking in case reports of this affection. The cases of Saundby[9] and Mott[10] should not be included in this group, for in both of them there was paralysis of the esophagus due to syphilitic nerve lesions rather than to syphilitic disease of the gullet itself.

Wile states that there is no apparent reason why the disease should become localized in the esophagus in the cases that have been reported. In no instance did injury seem to play any role, but in many of the cases there were specific lesions in the throat.

"The pathology of syphilitic esophagitis depends upon the time at which the case may be studied. Secondary superficial erosions and ulcerations, such as occur in the mouth and pharynx are not described in the esophagus. Such cases do not come to autopsy frequently. The not infrequent dysphagia, however, that occurs in secondary syphilis could, I think, well be due to superficial erosive syphilides. The great bulk of our cases, however, are those of tertiary syphilis. Here it would seem that the process is usually a gummatous condition of the submucosa which undergoes one of two changes. It may, under appropriate treatment, or even spontaneously, involute by fatty degeneration, such as is described by Lublinski and by West, the second case of Follin's, and in Clapton's case cited by West. In the event, however, of no treatment, or occasionally in spite of treatment, such gummatous changes are apt to undergo early ulceration. If these heal, there results a scar with a marked tendency to contraction and resulting stenosis. Finally there may be, instead of localized scarring and contraction, a diffuse process encircling the entire tube for the greater part of its length and causing almost complete stenosis and impassability for solid food."

The most important symptom of syphilitic esophageal stenosis is difficulty in swallowing, which as a rule develops gradually. At first there is slight difficulty in swallowing solid food, then solid food can be swallowed only in small bits, and finally not at all: later it becomes difficult to swallow even liquid food. Pain is usually not a marked symptom, except where there is active ulceration, and not always then. As secondary symptoms there result anemia, cachexia and the sequelæ consequent upon inability to eat.

The differential diagnosis may be very difficult, for carcinoma of the esophagus, pressure from mediastinal masses and spastic conditions must be ruled out. In addition it must always be remembered that it is possible that gummous changes might later become cancerous. Fluoroscopic examination with bismuth in the esophagus is of great value in some instances, and the signs of syphilis in other organs, or the presence of a positive Wassermann would be of considerable value. It is probable that more than one case of syphilis of the esophagus has been deemed cancerous and given up to die, when active measures might have saved life.

The treatment consists of antisyphilitic remedies and esophageal dilatation with suitable bougies.

Syphilis of the Stomach

Disturbances of the stomach during the early stages of syphilis have not received the attention they merit; the literature on the subject is extremely scanty. However, Neugebauer,[11] with true Teutonic industry, has examined the stomach contents of two hundred syphilitics in the secondary stage and found hypoacidity in 62 per cent, while in 18 there was a marked diminution of free hydrochloric acid. In 17 per cent hyperacidity was discovered. Local treatment of the stomach condition did not improve these findings, but treatment of the syphilis was followed by marked benefit. He states that all two hundred patients were healthy before the syphilis was acquired.

In twelve years experience with syphilitic patients I have seen five instances in which intractable vomiting accompanied the secondary lesions, although in no instance did the other symp-

toms seem to be especially severe. All of the cases cleared up under mercurial injections. Curiously enough I have had no similar cases since the introduction of arsphenamine, so have not had an opportunity to test that drug. In a large number of cases the patients complain of gastric disturbances during the florid period, and it is possible that in some instances this may be due to an eruption upon the walls of the stomach. Neugebauer's observations are of considerable value in showing that in some instances at least changes in the gastric juices may be responsible.

Tertiary syphilis of the stomach has been described by many men, since Andral[12] first described this disorder in 1834. Mathieu[13] has published an excellent historical review of gastric syphilis. The disease is almost universally conceded to be unusual, although the majority of writers opine that it is not as rare as thought. Autopsy findings upon syphilitics hardly bear out this statement. Symmers[14] in 314 autopsies upon syphilitic patients found but one instance of gastric lues. Chiari[15] in 243 autopsies found but two cases, and Stolper[16] and Fraenkel[17] had similar experiences. Aristoff,[18] however, states that careful histologic examination frequently reveals miliary gummata and diffuse inflammations of an undoubted syphilitic nature.

Clinically there are four types of the disease, first, syphilitic ulcer, second, gummata giving tumor masses, third, pyloric stenosis and fourth, diffuse infiltrations of the wall.

Cases of ulcer have been reported by McNeil,[19] Meyer,[20] Morgan,[21] Smithies,[22] Lockwood,[23] Downes and LeWald,[24] and many others. Ewald states that probably 10 per cent of all ulcers are of a syphilitic nature, but Morgan is sure that the figure should be much nearer one per cent. According to Kohn,[25] who has written one of the best articles upon the subject, these ulcers may exist alone, or may be associated with gummata. They may be multiple, although they are usually solitary. The site of predilection is the posterior aspect of the cardia and the pylorus. In shape they may be either round or oval, and in depth they vary from superficial erosions to those causing perforation. "Characteristic for this lesion are thickening of the mucosa and submucosa and nodules of infiltration followed by central necrosis, together with constant finding of endarteritis and endo-

phlebitis." The pathology of the condition is identical with that of tertiary syphilitic lesions in any portion of the body. It is possible that the lesions are not so apt to cause the presence of blood in the stomach contents as are true peptic ulcers.

Tumors have been reported by Kohn, Morgan, Einhorn,[26] Smithies, Downes and LeWald, and other observers. These growths are usually mistaken for carcinoma, inasmuch as the patients show symptoms that are very characteristic of malignancy. The growths sometimes reach a considerable size before ulceration occurs. The tumors are perhaps most common near the pylorus or upon the posterior surface of the cardia. Details of x-ray study of these growths may be found in the papers of Morgan, Smithies and Downes and LeWald, and also in Dr. Van Sweringen's article on x-ray diagnosis in this book.

Stenosis of the pylorus is, of course, brought about by the contraction of a scar resulting from a gumma, that has either broken down or healed, without ulceration, by fibrosis. Hubbard[27] has recently reported a typical case. In these cases it is often necessary to resort to surgical procedures unless the diagnosis is made early and proper treatment instituted, for even arsphenamine can not be expected to dissolve scar tissue.

Diffuse sclerosis or cirrhosis is due to a diffuse infiltration of the stomach walls, and may produce varying pictures, the dumb-bell-shaped stomach, a condition similar to sclerosing gastritis, to Brinton's linitis plastica, which in reality may always be syphilitic in nature, to a diffuse carcinomatosis of the stomach wall, to a diffuse hypertrophy of the entire organ on a tuberculous basis, or to stenosing gastritis. The case reported by Lafleur[28] still remains classical.

As is to be expected, all cases of syphilis of the stomach show certain things in common, and these have been well worked up by Smithies. The disease is most apt to manifest itself between the ages of thirty and sixty, it is almost as common in women as in men, it is usually a late manifestation, but may appear during the late secondaries, and usually manifests itself rather suddenly without previous digestive disturbances. The laboratory findings generally show some anemia; occult blood in the stool is rare; gastric acidity is usually low. Smithies thinks

that the Wolff-Junghans test may be of considerable value, and that the formol index as shown by the formaldehyde titration method suggested by Sörenson and Schiff might be of value in differentiating syphilis from cancer inasmuch as the index in cancer is much higher.

While time should never be lost in a case of suspected malignancy, still it should always be borne in mind that syphilis of the stomach can give all of the symptoms of cancer, and every patient who is suspected of suffering from gastric malignancy should have lues ruled out as a routine procedure.

Syphilis of the Intestines

Syphilitic lesions of the intestines are probably more common than those of the stomach, although there is a great paucity of literature on the subject. It is probably commoner in the congenital than in the acquired type of the disease. Chiari[29] failed to find a single instance in his 98 autopsies upon syphilitics. In a recent article Symmers[30] states: "In six subjects of the Bellevue Hospital series (314 cases), syphilitic lesions of the intestines were present. Ulcerative lesions of the cecum occurred once, and ulcerative and stenotic lesions of the colon five times. In one case the splenic flexure and the descending colon 6 cm. below were ulcerated and stenosed, and in the remaining four cases there were stenotic lesions in the rectum." It is, of course, a well-known fact that syphilis of the rectum is far from uncommon, especially in the tertiary form. The lesions usually consist of gummata that break down with consequent stenosis. Cases of intestinal syphilis have been reported by Fraenkel,[31] Hueter,[32] Gutman,[33] Homen,[34] Kohn[35] and others. It is to be noted that in the majority of instances the lower jejunum is the favorite site of ulcers, which tend to occur in groups and which are practically always annular in shape. However, in the case described by Arken[36] the lesions were very small and were distributed throughout the intestine. The presence of stenotic lesions could easily lead to the diagnosis of carcinoma. However in the vast majority of instances it is certain that surgical intervention is necessary to relieve the stenosis.

Syphilis of the Rectum

Considering that pederasty is not an unknown practice, chancres of the rectum are extremely rare; very much rarer than chancres of the anus. D'Arcy Power[37] has reported a case which was recorded by Hartley, where there was a typical chancre about one inch within the sphincter. Gradwohl[37a] has recently reported a case of chancre within the rectum. Lang[38] has examined forty-five men and sixty-five women in the florid stage of syphilis as to the presence of secondary lesions in the rectum and found them in sixteen instances, usually in the form of slight erosions seated upon the posterior wall. In these cases there were very few symptoms. There are four types of tertiary lesions: (1) a proliferating proctitis; (2) a diffuse interstitial inflammation known as "anal-rectal syphiloma;" (3) gummous inflammation; (4) diffuse fascial tumor of the pelvis.

Hamonic[39] has described a condition to which he gives the name of proliferating proctitis, because the mucous membrane develops fragile processes, which may be so numerous as to fill the rectum; strictures are said to have followed in some instances.

The ano-rectal syphiloma, first described by Fournier, is limited to the lowest part of the rectum, and produces stricture by the absorption and replacement of the syphilitic deposits by scar tissue. It is probable that this condition is simply a localized diffuse gummous process as Power suggests. Power further states: "An examination of the rectum in these cases shows that the wall is rigid and thickened either in its whole circumference, as is usual, or in parts only. The wall of the bowel has lost its resiliency and contractility. It feels thickened, and although the mucous membrane is smooth the wall of the rectum is often irregular and may be transversed by ridges of thickened tissue. The anus may share in these changes. * * *"

Gummous inflammation of the rectum occurs in two forms, the circumscribed and the diffuse. Gummata develop in the submucous tissue and vary in size from extremely small growths to those several inches in diameter, and they may be either single or multiple. They run the usual course of gummata elsewhere, tending to caseate, and rupture of the bowel may occur; when this occurs upon the anterior wall, a fistula may be formed into

the vagina of women or the bladder of men. Complete stricture probably does not follow, although there is sure to be some narrowing of the lumen.

The diffuse gummous process usually begins near the anus, and the entire circumference of the bowel is affected. Multiple ulcers may form from the breaking down of several foci. The disease is distinctly more common in women than in men. In the surgical service at Freedmen's Hospital I have seen at least a dozen cases in women and only two in men. The sphincters frequently lose their tone, and involuntary passage of feces and pus then occurs. The skin outside of the anus usually shows considerable irritation. When this condition heals there is left a ragged condition of the anal folds that has been compared to the wattles of a cock's comb. As healing takes place there is the formation of scar tissue and a stricture gradually forms. As a complication there may occur, especially in those in bad health, a phagedenic inflammation which may destroy much of the perineum. While Richerand[40] taught as early as 1812 that nonmalignant strictures of the rectum were due to "*condylomes internes*" it remained for Cornil,[41] Panas and Valtat,[42] Hartman and Toupet,[43] and some others to definitely prove that syphilis was the underlying cause of most cases on noncancerous rectal strictures. Patients suffering from stricture complain of constipation, often with alternating attacks of watery diarrhea. The diagnosis can usually be made by rectal examination, the characteristic finding being that the entire wall of the rectum is affected. This finding will usually suffice to rule out cancer. The treatment of these syphilitic lesions, if seen before stricture has taken place, is the general treatment of syphilis, together with local applications for cleansing purposes. Where stricture has occurred the treatment is entirely surgical, either local dilatation, or if necessary a colostomy.

The last type of rectal syphilis is that described by Herxheimer,[44] who cites four cases from the literature in addition to reporting one of his own. The pelvic fascia is chiefly involved, and the rectum only secondarily, there being a dense mass in which the organs are embedded.

Syphilis of the Liver

The liver is sometimes affected in secondary syphilis, and even more commonly in tertiary lues.

Secondary Syphilis.—In early syphilis there are two clinical manifestations that must be noted, first, jaundice, and second, acute yellow atrophy.

Syphilitic Jaundice.—The following account of syphilitic jaundice is taken chiefly from the monographs of Rolleston[45] and Oser.[46] Gubler[47] in 1853 first called attention to the association of jaundice with secondary syphilis in a memoir in which he reported five cases. Since then cases have been reported by Werner,[48] Lancereaux,[49] Lasch,[50] Quinke and Hoppe-Seyler,[51] Engel-Reimers,[52] Josef,[53] Thümmel[54] and others. It is rare, almost certainly occurring in less than one per cent of all cases showing marked secondary manifestations. Curiously enough it has been noted that the majority of cases show marked glandular enlargement, although, of course, this is not unusual in secondary syphilis. There are a number of theories as to its cause, first a syphilitic catarrhal cholangitis; second due to a condyloma of the bile duct; third pressure exerted by enlarged lymphatic glands on the portal fissure. Rolleston thinks it probable that it is due to a catarrhal condition of the small intrahepatic bile ducts, and that when the change is excessive it may run on into acute yellow atrophy. It would also seem possible that an autolysis of the liver cells themselves might produce it in some cases at least. There is no proof that jaundice is due to mercury, inasmuch as it is usually cured by the administration of this drug.

Clinically it is about as frequently seen in men as in women, usually comes on suddenly without any special disturbance, and coincides with the arrival of the secondary eruption. The jaundice is well marked and tends to become chronic unless there be antisyphilitic treatment. The liver is usually a trifle enlarged, and the spleen may be palpable, although as will be shown later, this is not especially rare in early syphilis. As a rule the prognosis is good, although in some rare cases acute yellow atrophy may supervene.

Acute Yellow Atrophy.—An especially valuable review of this rare but important complication of syphilis appeared as an editorial in the *Journal of the American Medical Association*[55] a few years ago, and I shall quote largely from it. In 1908 Fischer[56] collected fifty definite cases, and since that time others have been reported. There seem to be no particular features which distinguish these cases from those of the ordinary type of acute yellow atrophy. There are two possible causes for this usually, but not invariably, fatal complication. One is direct invasion of the liver by treponemata, or by the action of poisons from extrahepatic organisms, and the other is in the antisyphilitic medication. Attempts to find treponemata in the liver have generally failed, neither is there any evidence to show that there is an unusually large amount of toxin in the system. Acute yellow atrophy is essentially a rapid autolysis of liver substance; it has been demonstrated that both mercury and arsenical preparations can cause autolysis of the liver,[57] so it is possible that in some instances treatment may be the cause, but on the other hand this complication may supervene in cases that have not been treated,[58] as in one that I saw in Parker's service at the Freedmen's Hospital. Tileson[59] has reported a case where mercurial inunctions in a nonsyphilitic were followed by the development of acute yellow atrophy. Regarding the symptoms Osler[60] states: "The symptoms appear gradually, with loss of strength and appetite and anemia; vomiting and jaundice appear and, later, the cerebral symptoms of delirium, involuntary passage of urine and feces; the urine contains bile, leucin and tyrosin, and seldom more than a week elapses after the appearance of the more serious symptoms before death." It may be remarked in this connection that when one reads the literature he must be struck by the fact that in the vast majority of instances leucin and tyrosin could not be demonstrated in the urine. In the early stages the liver is usually enlarged, but later becomes much decreased in size. Concerning the pathology Adami[61] says: "The liver may be reduced to one-half its natural size, its consistency is increased, and the capsule thrown into folds, owing to the shrinkage of the parenchyma. On section, the surface is of a bright, lemon-yellow color, with patches of a darker brownish-red. The yellow areas are soft

and somewhat swollen, while the red are firmer and rather of a leathery consistency. Small hemorrhages are common throughout the substance. * * * Histologically, the parenchymatous cells in the yellow patches show extensive fatty changes, together with an accumulation of bile pigment and crystals of bilirubin. * * * The reddish areas are composed mainly of a network of capillaries, in the meshes of which can be seen isolated, degenerated liver cells, and a detritus of broken-down cells, fragmented nuclei, masses of pigment, chromatin and blood. Where death has been more than usually delayed, some evidences of regeneration can be made out.''

If such a condition be suspected the treatment is a matter of great importance, inasmuch as in some cases necrosis may be due to either mercury or arsenic. If the patient has been receiving arsphenamine this should be discontinued at once and mercury substituted, and vice versa. If the patient has been receiving no antisyphilitic medication, small doses of arsphenamine should be administered every two or three days.

Tertiary Syphilis of the Liver.—That syphilis of the liver is by no means infrequent during the late stages of syphilis is evidenced by various autopsy reports. Symmers,[62] who reported 314 autopsies upon syphilitic subjects found syphilis of the liver 105 times. The older records do not show such a large number of cases of liver lues. For instance, Flexner[63] in reporting 5088 necropsies found 88 cases of hepatic syphilis, while Osler[64] states that in eighteen years at the Johns Hopkins Hospital but 30 cases were diagnosed during life, and that but 40 were recognized at autopsy. At the same time it must be remembered that these records were before the days of the Wassermann, and that at that time syphilis was not recognized to be as prevalent as it is today, hence many cases have undoubtedly escaped discovery, both in the ward, private room, and upon the autopsy table.

Rolleston[65] remarks that most of the cases of hepatic syphilis are found between the ages of twenty-five and fifty. McCrae[66] states that in Johns Hopkins Hospital series the excessive use of alcohol could not be excluded in any of the cases, and considers that drinking may be a contributory factor. Men are more frequently affected than are women, as is to be expected.

Rolleston states that for convenience the clinical manifestations of late hepatic syphilis may be grouped under the following heads:

I. Where the symptoms suggest portal cirrhosis, or simple chronic peritonitis and perihepatitis.

II. Presenting the features of widespread lardaceous disease.

III. Suggesting tumor of the liver, such as malignant growth, hydatid, or enlarged gall bladder.

IV. Imitating suppuration of the liver.

V. Resembling cholelithiasis.

VI. Resembling chronic splenic anemia.

VII. Where the clinical features resemble hypertrophic biliary cirrhosis.

To these seven groups Osler has added an eighth, where the symptoms are those of leukemia.

I. Cases imitating cirrhosis. These cases are far the commonest, and there are many reports of cases in the literature. It is probable that the reports of cured cases of cirrhosis of the liver are based upon syphilitic lesions in many instances. Usually there is a serous ascites, but this may be either chyliform or even hemorrhagic. As a rule other signs of portal obstruction are less marked than in true cirrhosis. Jaundice is rare. The ascites is probably produced by pressure on the portal vein, but in some instances by a local peritonitis, due to a superficial gumma. At first the liver is enlarged, but as contraction takes place due to scar tissue replacing gummata the liver becomes smaller. It is highly probable that many cases of atrophic cirrhosis are due to syphilis; in fact Symmers says that in about 80 per cent of all cases diagnosed as atrophic cirrhosis the Wassermann was positive.

II. Rolleston states that at times there may be a gumma in the liver associated with lardaceous disease (amyloid degeneration). The presence of an enlarged spleen and of a marked albuminuria would make one suspect the more serious condition. Rolleston reports a very interesting case where the two were combined.

III. Solitary or multiple large gummata not infrequently imitate malignant nodules in the liver, and there can be no doubt that many a patient has not had the proper treatment, because

malignancy was diagnosed. Gummata are usually situated upon the anterior surface of the liver, so that the tumor masses are more easily defined than in carcinoma, which is apt to start deep in the liver substance. Then too cancer nodules usually grow steadily, while gummata reach a certain point and then begin to contract. The use of arsphenamine should settle the question rather speedily, even if the laboratory findings do not, for it must always be borne in mind that cancer may develop in a syphilitic patient. An enlarged spleen always points to syphilis. Albuminuria also points to syphilis, as it is frequently an evidence of lardaceous changes.

IV. Cases with fever, resembling hepatic suppuration, have been discussed rather fully by Edwards.[67] The fever may suggest sepsis, hepatic abscess, malaria, tuberculosis or even typhoid fever, but is almost invariably ameliorated by specific treatment. Secondary infection may, of course, take place in a gumma, so that a primary abscess is closely imitated. Abscess, following amebic infection, may be difficult to rule out except by the therapeutic test.

V. Cases of syphilis resembling gallstones have been studied by Riedel,[68] among others.[69] Jaundice is not common in hepatic syphilis, but occasionally the pressure of a gumma or the drag of scar tissue upon the portal fissure may lead to this phenomenon. In rare cases this jaundice may be accompanied by colicky pains that suggest gallstones. Occasionally a gumma will simulate a distended gallbladder, as in the case reported by Parker.[70]

VI. In some cases of syphilitic disease of the liver the spleen may be enlarged, either as a direct result of secondary syphilis, as Wile[71] has shown, from amyloid changes, or from gummata, while the liver may be but little enlarged. If an anemia accompanies such a picture, it is but natural that a diagnosis of splenic anemia may be made as in the cases of Coupland[72] and Osler.[73]

VII. In very exceptional instances syphilis of the liver may lead to an enlarged liver with chronic jaundice and splenic enlargement as pointed out by Hanot.[74] As a rule the progress of the case is more rapid than in biliary cirrhosis, and the spleen is not so large. Lancereaux[75] has also written in regard to this

type, holding that some of the cases may be examples of leukemia.

VIII. Osler[76] reports the following case as an example of a case of hepatic lues resembling leukemia:

The patient was a woman of twenty-three who was admitted because of ascites. She had been a delicate child. Eight years before admission she had some abdominal troubles, since which time her abdomen had been enlarged. The present illness started two weeks before admission with a chill, shortness of breath, and pain in the left side. The examination showed a poorly nourished, anemic girl. The temperature was 103.5°, pulse 120 and respirations 36. Both liver and spleen were markedly enlarged, and the peripheral lymph glands were likewise enlarged, even the epitrochlear. The red blood count was 2,234,000 and the white nearly 100,000. At autopsy gummata of the liver were found.

Pathologically the following changes may be found in the liver in the course of late syphilis: gummata, cicatrices from gummata, perihepatitis, amyloid change, cirrhosis, thrombosis of the venous systems and infarcts. Gummata commence around the blood vessels just as they do in other organs, and run just the same course, that is, they are later replaced by fibrous tissue, and the extent of this scar tissue depends upon the size and number of the gummata. Cicatrices may produce stenosis of the bile duct, the cystic duct or even the hepatic duct, or the vascular supply may be interfered with so that localized necrosis follows. Perihepatitis may vary between a small localized thickening of the capsule, comparable to a "milk spot" on the pericardium, to a great thickening of the whole capsule, and even cause adherence to the body wall. In amyloid change the liver is enlarged, and resembles the amyloid changes from other causes. On cross section there is a marked transparent look, and the usual reactions with iodine and sulphuric acid are given. In the true hepatic cirrhosis there is usually a deposit of fibrous tissue between the acini, in which vessels with changes in their coats can plainly be seen. This is due to many minute miliary gummata which have resolved, leaving a diffuse sclerosis behind. In another type of cirrhosis, which resembles Laennec's cirrhosis there are isolated bands of fibrous tissue which divide the liver substance into islands. To the naked eye

one of the most characteristic types of hepatic lues is the hepar lobatum, where the liver is the seat of numerous depressed scars, so that the surface resembles a cobblestone paving.

Syphilis of the Pancreas

The subject of syphilis of the pancreas is most assuredly not well understood at the present time, although from time to time some light is being shed upon it. The subject of changes in the pancreas during secondary syphilis has been almost entirely ignored, although one might naturally expect that there might be tissue changes more or less analogous to those that sometimes occur in the salivary glands or in the liver. As bearing upon this point Laurent[77] has reported a very interesting case which he states was published by Tzizakow, where a glycosuria developing early in the course of syphilis was cured by mercury. Unfortunately I have been unable to obtain the original reference.

If one were to judge of the frequency of tertiary syphilis of the pancreas from the accounts published in the various systems of medicine and the various treatises, he would gather that some one had once thought that a distant acquaintance of his had once mentioned that a gumma might occur. However, that syphilis of the pancreas is by no means rare is proved by the late report of Walter-Sallis[78] and the still later work of Warthin.[79] Oser,[80] some years ago, distinctly stated that chronic indurative pancreatitis was at times due to syphilis, although most frequently in the congenital form of the disease. He mentions cases of Drozda, Hansemann and Dieckhoff to show that the same condition may be found in acquired syphilis. Walter-Sallis states that from the standpoint of pathologic anatomy, there are three forms of this affection: (1) inflammatory, scleroindurative, usually leading to atrophy; (2) gummous; (3) sclerotic gummous. As a matter of fact, all of these forms must be simply different stages or different degrees of severity of the same gummous process. He does not think that the clinical symptoms are as yet thoroughly understood, although he reports fifteen cases. The symptoms were usually those of other inflammations of the pancreas, digestive disturbance, steatorrhea,

jaundice, pain, and swelling. Fever was usually present. Fey[81] has reported a well worked up case. From the standpoint of pathology, the recent article by Warthin is extremely suggestive, although it is only a preliminary report. Warthin is especially interested in the question of diabetes and syphilis, and quotes authors to prove that nearly 10 per cent of paretics show sugar at some time, and further that many clinicians report (verbally) that it is by no means unusual to find syphilis and diabetes coexisting. He further states that since 1907 there have been at the University of Michigan six autopsies upon diabetic patients, and that all six of these showed undoubted histologic evidences of syphilis. The following changes were found in the pancreas of each case: fatty atrophy, especially in the body and tail; increase of inter- and intralobular stromata, especially along the ducts between the acini; inflammatory infiltrations both in the connective tissue and in the lobules, the infiltrate consisting of small round and plasma cells, and similar to syphilitic infiltrations in heart muscle; degenerative changes in the Islands of Langerhans; the presence of some atrophic acini; newly formed islands of acini arising from the ducts; sclerosis of the blood vessels; ducts with dilated and thickened walls; in one case treponemata were found in the pancreas. Warthin has further studied thirty-nine cases of syphilis and has found that the pancreas was not normal in a single one of these cases, in every instance changes somewhat similar to those just mentioned being found. Warthin concludes: "It seems very probable, therefore, that latent syphilis is the chief factor in the production of the form of pancreatitis most frequently associated with diabetes, but that diabetes is not always coincident with severe degrees of this type of pancreatitis."

Rosenbloom[82] has recently reviewed the relationship between diabetes mellitus and clinical syphilis, and after a study of his own cases and of the literature has come to the conclusion that in the vast majority of instances the syphilitic infection is not responsible. Personally I have found diabetes to be much more common in syphilitics than in the skin cases that come to my office. Unquestionably diabetes is more common where there is syphilitic disease of the central nervous system than in other types of lues.

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CHAPTER XIII

SYPHILIS OF THE VASCULAR SYSTEM

As Fordyce[1] has insisted, and as I have attempted to point out in this volume, syphilis is primarily a disease of the blood vessels. Even in the chancre the primary lesion is an endarteritis and a panarteritis. This is true in all other stages of syphilis, the lesions usually beginning in the perivascular lymph spaces. A granuloma speedily results, a granuloma characterized by the presence of small mononuclear and plasma cells, with a formation of new capillaries and fixed connective tissue elements. Giant cells may be found. Gumma formation is simply due to a breaking down of the tissues because they are less resistant to the action of the treponema. When one remembers these facts it is not surprising that syphilis of the vascular system is daily becoming more important.

Syphilis of the Heart

It is becoming a matter not only of clinical but also of autopsy record that the heart is frequently involved in syphilis. Fifteen years ago Grassman[2] wrote that in 288 cases of secondary syphilis marked disturbances of rate and rhythm occurred in 85 per cent and murmurs in 40 per cent. Cabot[3] found that in 562 patients suffering from heart disease syphilis was probably responsible in seventy-four. Practically all observers are agreed that aortic insufficiency is most often caused by syphilis, and Warthin[4] has shown that it plays a great part in the production of myocarditis. Autopsy records bear out the clinical findings remarkably well. Symmers[5] has performed autopsies upon 314 cases of late acquired lues and has found that the aortic valves were sclerotic in sixty-four instances, which figures agree closely with those of Longcope. Harlow Brooks[6] in 50 consecutive autopsies upon syphilitic patients with heart disease found that the pericardium was diseased 28 times, the myocardium 44 times, that true cardiac gumma was present 5 times, and that in 35 instances disease of the coronary arteries was present. Warthin,[7] in a late

article, states that in autopsies upon 41 syphilitic subjects active syphilitic disease was found in the heart in 36 cases. It should be especially emphasized that these lesions can frequently be found microscopically when they can not be recognized in the gross specimens, hence it is certain that the previous reports of autopsy findings in syphilis by no means cover all instances of syphilitic cardiac disease.

The syphilitic changes in the heart may be classified as follows:[8] Pericarditis; myocarditis; endocarditis; valvular disease; disease of the coronary arteries; angina; cardiac aneurysm; heart block.

Pericardial Syphilis.—Brooks[6] states that he found pericardial changes in twenty-eight out of 50 syphilitic hearts. He states that opalescent patches of thickening appear at the perforation points of the terminal arterioles. "These opacities are formed of a mingled fibrous and endothelial hyperplasia which apparently occurs chiefly about the terminal arterioles. The lesion is not confined to lues, but is more frequent in it than in any other one condition that I have yet observed, and I have compared its genesis to that of syphilitic leucoplakia so frequently seen, especially in the buccal mucosa." Adami and Nicholls[9] state that "milk spots" are found in 14 per cent of all autopsies, and that they are the results of intermittent pressure.

Myocardial Syphilis.—As already pointed out, Grassman[2] has insisted that myocardial disturbances may occur early in the course of syphilis. While clinically it is rather unusual to find marked early cardiac disease, yet such may occur; only recently I have seen a case in a physician where a serious myocarditis developed even before the secondaries became manifest. In 1898 Adler[10] called attention to the association of myocardial lesions with syphilis, he being one of the very earliest clinicians to note this complication. Warthin in particular has pointed out how frequently the myocardium is invaded. Clinically the manifestations may appear either in the course of the secondaries or late in the course of the disease. Anders[11] and Brooks[12] have well described the condition found upon clinical examination. If the disease develops during the secondary stage, the principal features are arrhythmia, particularly intermittence and tachycardia, and at times extrasystoles. The irregularity becomes more

marked after mild exercise or through nervous fear. Precordial pain is not common, and various writers disagree as to the amount of dyspnea present. Cyanosis frequently occurs. These manifestations are not characteristic of syphilis, as they may occur in any other form of myocarditis. However, they will usually disappear if antisyphilitic medication be pushed. In the late stages of syphilis the manifestations are those of myocarditis due to other causes. While the condition is difficult to diagnose in the absence of a positive Wassermann, Anders states: "Certain clinical peculiarities already mentioned may, however, serve to arouse suspicion of syphilis. Of these the tonelessness of the first heart sound and the decidedly irregular, accentuated character of the arrhythmia deserve special mention." Other excellent articles upon the clinical aspects of this complication are those of Brooks and Carroll,[13] Stockman,[14] Rosenfeld,[15] Callender,[16] Huchard and Flessinger,[17] Bricourt,[18] Mracek[19] and Landlois,[20] the last of whom gives an excellent bibliography of the German literature. While most of the literature, of which the article by Brooks and Carroll[13] is an excellent example, insist that myocardits is due to a periarteritis of the coronary vessels with a secondary myocarditis, Warthin[4] has definitely proved that syphilitic myocarditis may be primary. Warthin divides the lesions into two classes, the parenchymatous and the interstitial. Under the former head he groups pale degeneration of heart muscle, fatty degeneration, simple atrophy and necrosis. In the interstitial group he puts edema, interstitial proliferation, and myxoma-like areas. In all of these lesions he has been able to demonstrate treponemata by the original Levaditi method. He has further shown that the organisms may be found in large colonies without recognizable tissue reactions. The pale degeneration of the muscle substance may be recognized by its failure to take eosin properly, and by the loss of the striations. "In the severe grades of this change the muscle passes so insensibly into the connective tissue that it is difficult to separate the two." This form of degeneration is frequently associated with interstitial changes. Warthin further states that fatty degeneration of the muscles is often the only lesion to be discovered; the fibers are atrophic and are filled with fat globules. Calcium deposits may follow such fatty change. In simple atrophy the fibers are

simply decreased in size, while the interstitial tissue may or may not be changed. Necrosis is usually found in virulent congenital affections, and the muscles have undergone a liquefaction. "Such changes are absolutely independent of any vascular changes, and are wholly the result of the spirochetes that lie packed in great numbers in these necrotic areas." Edema is likewise more prevalent in congenital syphilis. Pale areas, moist and translucent, may be seen with the naked eye. Microscopically the fibers are pushed apart and the number of wandering cells is increased. Fat vacuoles can usually be found in the muscle fibers. These edematous areas are filled with organisms. The interstitial proliferation always is perivascular in origin and the lesions are those characteristic of other syphilitic lesions. Myxoma-like areas are found in the hearts of congenital syphilitics and are filled with treponemata.

Syphilitic Endocarditis and Valvular Disease.—For some time various writers have pointed out that aortic insufficiency and aortic endocarditis are frequently associated with syphilis. In this connection the work of Siehe and Saathoff,[21] Albrecht,[22] Citron,[23] Longcope,[24] Babcock,[25] Collins and Sachs,[26] Anders[27] and many others must be noted. The work of these men, which has been similar to our experience in the wards of the Freedman's Hospital, definitely proves that over 75 per cent of all cases of aortic insufficiency occur in syphilitics. While it is probable that there are other causes of aortic disease, still it is certain that syphilis is the chief factor in the production of this lesion. Aortic insufficiency, developing in the young, is almost certain to be of specific origin. On the other hand, it is probable that syphilis but rarely causes other forms of valvular trouble. Longcope has emphasized the association of aortic insufficiency with aortitis, especially the mesaortitis of syphilis. The mere fact that a patient has complained of rheumatic pains is no reason for making a diagnosis of rheumatic origin for a heart lesion; syphilis frequently causes arthritic symptoms. Anders states that the lesion usually develops in from two to three years after infection. He further states: "Severe pains may attend an invasion of the valve segments often accompanied by angina pectoris from implication of the coronaries in early cases, developing more or less acutely. If the specific character of the cause

be overlooked, and inappropriate or the usual routine treatment of chronic valvulitis be adopted, these cases may reach an early fatal termination. On the other hand, intensive antisyphilitic treatment may, if instituted early, bring about marked improvement, and the cases progress as aortic incompetency due to other causes.'' Anders considers that in syphilitic aortic insufficiency the arrhythmia is more marked than usual. Sachs[28] states that the left ventricle is not so enlarged as is usual in other types of the disease, and that the capillary pulsation is therefore less.

Disease of the Coronary Arteries.—Brooks[20] states that in 50 autopsies performed upon syphilitic heart patients he found that in 35 instances the disease of the coronary vessels was greater than the general arterial disease. He considers that syphilis has a special predilection for these vessels, and that they may be attacked even before the secondary rash appears. ''The type of coronary change is variable. In three instances coronary thrombosis had resulted from an active primary endarteritis, but the most frequent change appears to be a fatty degeneration with endarteritis. From the diseased vessels there spreads out into the muscle all sorts of changes, from a granulomatous and true myocarditis to fibrosis and necrosis, the result of deficient nourishment.'' The symptoms are similar to those described in the section upon myocarditis, except that there may be rather more pain.

Angina.—As has already been pointed out, syphilis frequently affects the coronary vessels, and as a result anginal pains are not at all uncommon, especially in myocarditis. The vessels may be completely closed by endarteritic processes, and then true angina may result. Anders[30] states that he has collected 270 cases of angina pectoris from the literature, of which 72 gave evidence of syphilis. Anders continues: ''This percentage, however, is much too small, since in 250 of the recorded instances no mention was made of a Wassermann test, sole dependence being placed in the history.'' Anders is sure that syphilis is responsible for many cases. Breitman[31] writes: ''Every case of angina pectoris during the younger period of life is open to suspicion of syphilitic origin.'' Moon[32] considers that the vast majority of cases of angina are associated with syphilis. Saundby[33] feels that congenital syphilis is responsible for some of the cases in the

young. Osler[34] considers it an important cause, especially in persons under forty. In these days when angina has become such a fashionable disease, it is nothing less than criminal for the physician to neglect the possibility of syphilis.

Heart Block.—The condition known as heart block or Stokes-Adams' disease is due to the failure of the ventricle to contract each time that the auricle does. This is because the bundle of His fails in its conductivity. That this failure may be due to syphilis of the bundle has been definitely established by many men. Ashton, Norris and Lavenson[35] some years ago presented a comprehensive review of the subject, in addition to reporting a case where autopsy revealed a gumma in the bundle of His. Similar cases have been reported by Grünbaum,[36] Keith and Miller[37] and Handford.[38] Anders[39] quotes Robinson as having found syphilis present six times out of sixteen cases. Jagic[40] has recorded a case proved at autopsy. Brooks[41] states that in five cases syphilis was present in all. Recently I have seen a case in a man of thirty-nine, where the Wassermann was negative, but where the luetin was strongly positive although no iodides had been administered. Arsphenamine in small repeated doses speedily cleared up the condition.

Aneurysm of the Heart.—Aneurysm of the heart wall is unusual, but does occur, as Brooks[42] has found it in three instances out of fifty autopsies upon patients with syphilitic heart lesions. Hence syphilis is probably the commonest cause, if not the only cause, barring trauma, of this disturbance. Osler[43] states that the left ventricle near the apex is the usual seat of aneurysm. Ultimately a large rounded tumor may protrude from the side of the heart wall.

Treatment of Syphilis of the Heart.—The subject of treatment of cardiac syphilis has been especially considered by Brooks and Carroll[44] and by Anders.[45] It must, of course, be understood, that when once tissue is destroyed by syphilis it can not be replaced, even by arsphenamine, which is so frequently considered a panacea in any disturbance due to syphilis. However, before syphilitic destruction of tissue has taken place vigorous antisyphilitic treatment may do the greatest amount of good, often resulting in a complete and brilliant cure, for the time being at least. It is universally agreed that both arsphenamine and mer-

cury should be administered, while regarding the utility of the iodides there is a healthy skepticism. Some authorities feel that the arsphenamine should always be administered intramuscularly, upon which point I beg to disagree, inasmuch as the pain that is frequently caused by such injections seems to me to be an extremely bad thing for patients with heart manifestations. On the other hand, I know from personal experience, that such patients bear intravenous injections well. Personally I administer about two-thirds of a full dose about every week, while mercury is given in full doses by intramuscular injection. In urgent cases the arsphenamine may be given even more frequently. A competent internist should always have charge of such a patient, and direct the medication for the heart condition itself, for digitalis or some other of the cardiac stimulants may frequently be employed to advantage.

Aortitis.—Within the past few years the subject of syphilitic aortitis has been attracting much and merited attention. For many years it has been recognized that syphilis is a factor in the production of aneurysm, but it was not until the work of Döhle[46] in 1888 that the direct connection between the two was proved. Other excellent early accounts were those of Huchard,[47] Dieulafoy,[48] Gallavardin,[49] Fournier,[50] Corrigan,[51] and Albutt.[52] In 1903 the works of Chiari,[53] Benda[54] and Marchand[55] attracted new attention to this disease. Since that time excellent articles have appeared from the pens of Bruce,[56] Schwartz,[57] Breitmann,[58] Goldschneider,[59] Fahr,[60] Herxheimer,[61] Longcope,[62] Symmers and Wallace,[63] Fordyce[64] and others.

That many syphilitics suffer from this condition is made manifest by the autopsy experiences of Symmers,[65] who found that in autopsies performed upon 314 cases of late acquired syphilis, aortitis was found in 175 instances. In this series the arch alone was affected 109 times, while the entire aorta was diseased 49 times, with combined lesions in 29 instances. Other pathologists recognize the condition as an extremely common one, ranking with heart, testicle, and adrenal lesions in frequency.

The disease is much more common in men than in women, at least 80 per cent of the cases occurring in the male sex. The lesion usually develops before the patient is 50 years of age, the average age being a little over 40. The disease is noted as being

especially prevalent in negroes, which coincides with Janeway's[66] figures and with our own experiences in Washington. Longcope thinks that the disease usually develops about fifteen years after

Fig. 97.—This shows a generally dilated aorta in walls of which are numerous foci of more severe damage at which secondary dilatations have occurred. Multiple secondary aneurysms. One of these small aneurysms has perforated into the superior vena cava (X). (Courtesy of Dr. Paul G. Woolley.)

the initial lesion, although it may, of course, make its appearance at a much earlier date. Certain authors feel that free indulgence in alcohol may be a predisposing factor. Since most of the cases occur in men who have done hard work, it is possible

that heavy exertion is a predisposing factor to be considered.

The symptoms which have attracted the attention of every writer on the subject are pain, dyspnea, palpitation, and tachycardia. The patient usually complains of a dull, either constant or intermittent pain beneath the sternum. However, anginal pains are far from uncommon. In most of the cases there is

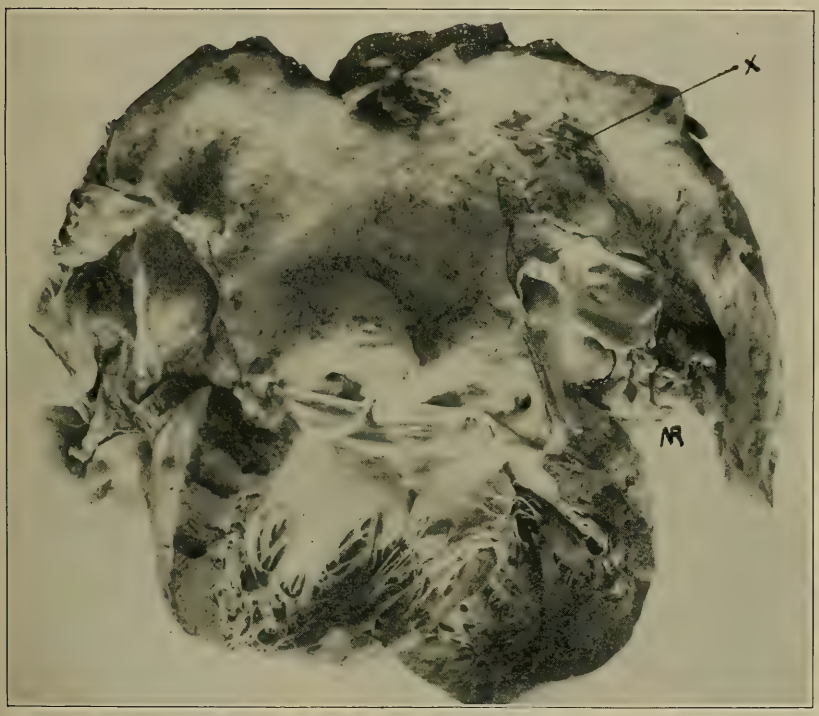

Fig. 98.—Diffuse mesaortitis of the luetic type. Diffuse aortic dilatation. Incipient aneurysm (X). Thrombosis of the innominate and carotid arteries. (Courtesy of Dr. Paul G. Woolley.)

dyspnea upon slight exertion, and this often becomes worse, especially if aortic insufficiency supervenes as it is so apt to do. In other instances the dyspnea may be paroxysmal in character, coming on in attacks which may last from five to fifteen minutes. The dyspnea is prone to be expiratory in character. In some few instances aortitis may cause a continued fever as Popoff[67] has pointed out. By some cyanosis is said to be common.

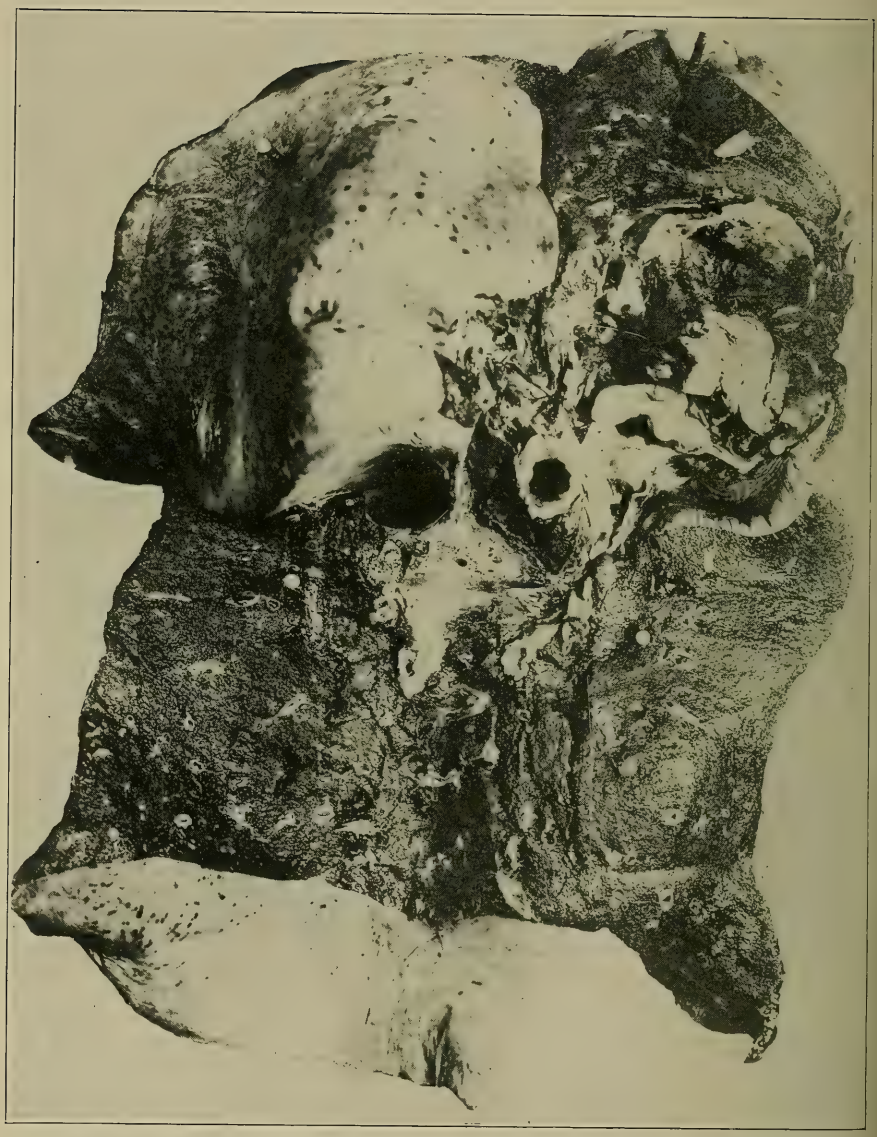

Fig. 99.—Photograph of left lung showing the opened aneurysmal sac of the main branch of pulmonary artery in upper lobe. Lying in the sac is a laminated blood clot. Just below the aneurysm, to the right of the branches, the slit-open dilated pulmonary artery shows very well the sclerosis of the wall. Throughout the entire lung the smaller branches of the arteries show marked sclerosis. (Courtesy of Dr. Aldred Scott Warthin.)

The commonest complications are aortic insufficiency, angina pectoris and aneurysm. As already pointed out, aortic insufficiency is an extremely common complication, in fact it may be looked upon as the natural result of practically all cases of aortitis. Probably from one-fifth to one-sixth of the cases develop an aortic dilatation, often sufficiently large to be called an aneurysm.

In making the diagnosis the symptoms are of great importance. Next ranks a positive Wassermann reaction, at least in the cases that do not show a dilatation of the aorta. Where the aorta is dilated, x-ray examination is of the greatest possible assistance, although some care must be used in interpreting the shadows. McCrae[68] has written an excellent article upon the physical diagnosis of aortic dilatation. The most important signs are an abnormal pulsation in the subclavian and carotid arteries, with an impulse in the episternal notch. There may be a heave beneath the manubrium or pulsation in the first and second interspaces. The veins of the neck are sometimes dilated. A rough systolic murmur is often heard at the aortic cartilage; this may be the first physical sign. In a few instances pressure effects are present. However, Longcope calls attention to the fact that aortic dilatation does not necessarily mean syphilitic aortitis, as it may follow aortic insufficiency due to rheumatism.

The prognosis, in hospital cases at least, is rather bad, the majority of the patients dying within five years of the time that the diagnosis is made. In private patients who can take good care of themselves and do not neglect treatment, the outlook should be much better, although probably never too good.

Fordyce well discusses the pathology of the condition. "The inner surface shows isolated or confluent elevated, wrinkled, grayish, and translucent sclerous areas, with puckering or cicatricial pitting, or again radiating ridges with depressed cicatrices between. The intima over the affected areas preserves its glistening appearance. The thickness of the artery varies in different portions, so that while indurated and sclerotic at one point, it is thin and translucent at another. Depending on the extent of involvement, dilatation is present. This may be uniform throughout the length of the thoracic portion, or appear as small aneurysmal pouchings or a true saccular aneurysm. All

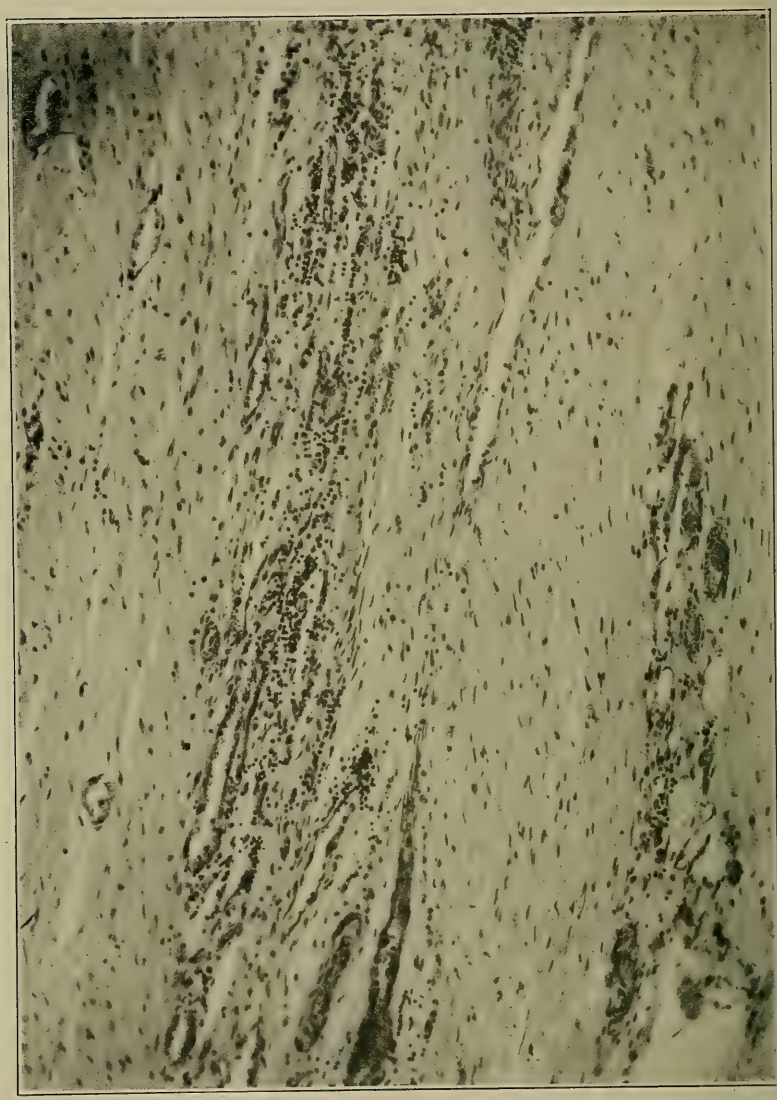

Fig. 100.—Early stage of aortitis, showing characteristic lymphocytic and plasma-cell infiltration about the small vessels in the adventitia. (Collection of Dr. John A. Fordyce.)

degrees of transition are found. Ordinarily it is not difficult to differentiate this condition from arteriosclerosis in the absence of fatty degeneration and calcification. However, in old subjects there may be a combination.

Fig. 101.—Later stage of aortitis, showing advanced sclerosis of the vessel walls. (Collection of Dr. John A. Fordyce.)

"In the beginning the lesion is often confined to the vessel in proximity to the aortic valves. Later it extends to them and gives rise to insufficiency, which condition is very frequent. With the extension of the process the ascending aorta and the arch are involved. Not rarely changes are also noted about the

mouths of the larger branches of the arch, causing narrowing of the left carotid, innominate and subclavian arteries, which localization is significant from a clinical point of view. With involvement of the aortic ring the mouths of the coronary arteries are also considerably reduced."

The demonstration of the presence of treponemata in these lesions by Benda,[69] Reuter,[70] Schmorl,[71] Wright and Richardson[72] and Longcope and Cook[73] has settled any possible question as to the syphilitic nature of these lesions, even although Symmers, Crowell,[74] Aschoff[75] and Brown[76] have failed to find them. In addition Fordyce has proved that the histopathologic picture is unmistakably that of syphilis. The disease begins in the adventitia, but the most striking changes are in the media. Miliary gummata are first formed, these undergo necrosis, and are replaced by scar tissue. In fresh cases there may be found about the vasa vasorum of the adventitia an inflammatory exudate of lymphoid and plasma cells, the nutrient vessels themselves undergo an obliterative endarteritis. The elastic tissue is either fragmented or entirely absent. The intima either shows no change or a compensatory thickening. It is still a disputed question as to whether or not the changes are primary in the media or in the vasa vasorum.

As regards treatment there is still considerable difference of opinion as to the efficacy of antisyphilitic medication. In this connection we should always remember that there are two conditions present, first, a syphilitic infection with localized syphilitic lesions in the aorta, and second, a damaged arterial wall, which we can not hope to repair. Certain it is that arsphenamine will often render the patient much more comfortable and frequently totally remove a distressing amount of pain. When arsphenamine was first introduced Ehrlich warned against its use in patients suffering from cardiovascular lesions. At the present time, however, no fear need be felt of employing it in these conditions. This point is proved by the writing of Longcope, Weintraud and others, and is a point now generally well recognized by all experienced clinicians. It is still barely possible, although not probable, that there may be some danger when there is disease of the coronaries, so it is just as well not to give more than 0.4 grams of arsphenamine. Unquestionably in the vast

majority of instances arsphenamine therapy should always be combined with mercurial treatment as well. Certain it is that much relief can nearly always be promised, and frequently nearly all of the symptoms will disappear. It is highly probable that if the patient can refrain from heavy work there is not the danger of the formation of an aneurysm that there would otherwise be.

Unquestionably all cases suffering from late syphilis, either active or latent, should have a study made of their aortas. In this way much trouble could undoubtedly be averted. Whether or not there are any symptoms, a fluoroscopic or radiographic examination should be made.

Peripheral Arteritis

When one considers that syphilis of the aorta and of the cerebral vessels is so common, he must be surprised at the paucity of the authentic literature dealing with syphilitic arteritis of the smaller vessels. In the literature there is still great confusion, for the lesions produced by such disturbances are very similar to those found in Raynaud's disease and in thromboangiitis obliterans of Buerger.[77] That syphilis can affect other arteries than those above mentioned is definitely proved and the presence of aneurysms of various arteries also bears out this statement. In the peripheral types of syphilitic arteritis the lesions would naturally be those due to disturbed circulation, and would consist of either anemia or possibly cyanosis, according to the extent of the lesions and the quantity of the peripheral circulation. Gangrene would naturally result in the severe cases. The lesions should but rarely be symmetrical. Diagnostic points should be the presence of a positive Wassermann reaction, and the therapeutic test, namely the subsidence of symptoms when antisyphilitic medication is applied. However, neither of these tests is absolutely conclusive, and to definitely prove the case at the present writing treponemata should be found in the arterial walls, or possibly the histopathologic picture should be that eminently characteristic of syphilis.

Syphilitic arteritis must be distinguished from thrombosis of an artery due to other causes, from Raynaud's disease and from

thromboangiitis obliterans. Spontaneous thrombosis is rare, is usually unilateral, the Wassermann is negative, and the condition does not clear up under antisyphilitic medication. In Raynaud's disease the condition usually is characterized at first by paroxysmal attacks, between which there are periods of perfect health. The disease is almost always symmetrical, and it is not unusual for the nose, ears or cheeks to be affected. The pulse in the artery is not lost, inasmuch as there is no thrombosis. In thromboangiitis obliterans the following symptoms are usually found; the disease almost invariably occurs in Russians; the pulse is lost, the vessels chiefly affected being the dorsalis pedis, posterior tibial and popliteal, more rarely the femoral, radial and ulnar; the typical symptoms associated with impaired circulation; true vasomotor disturbances of transitory nature; severe pain or intermittent claudication; slow course that is steadily progressive and a peculiar type of migrating phlebitis in the course of either the external or internal saphenous in about 20 per cent of the cases. Males are usually affected.

Cases of arteritis supposedly due to syphilis have been reported by Hutchinson,[78] Darling and Clark,[79] Etiénne and Lucien,[80] Ravogli,[81] Klotz,[82] Durandard,[83] Lang,[84] D'Ornellas,[85] Leudet,[86] Jacoby,[87] Sée,[88] Nash,[89] Fournier,[90] Nordman,[91] Thibiérge[92] and others.

Raynaud's Disease

As already indicated in the preceding section on syphilitic peripheral arteritis, the greatest confusion exists in the literature between Raynaud's disease and syphilitic arteritis. Lisser [93] has recently completely reviewed the subject of Raynaud's disease due to syphilis, and has given a full bibliography to date. One of the best accounts of the clinical manifestations is that of Osler,[94] who states: "There are various grades of the disease, of which mild, moderate and severe types may be recognized. In the mild forms the disease never gets beyond the stage of such vascular disturbance as is frequently seen in chilblains. The hands alone may be affected—more often the hands and feet. In the winter, on the slightest exposure, there is acrocyanosis, which gives place in the warmth to active hyperemia. * * *

"The condition may persist for years and never pass to

necrosis. In a case of moderate severity, a woman, aged say twenty-five or thirty, after a period of worry or ill health, has pains in the fingers, or a numbness and tingling; then she notices that they are white and cold, and in an hour or so they become red and hot. Within a day or two a change occurs; they remain permanently blue perhaps as far as the second joint or knuckles. * * * The cyanosis persists and the tip of one finger or the terminal joint of another gets darker and a few blebs form. The other fingers show signs of restored circulation, but necrosis has occurred in the pad of one finger, and perhaps the terminal inch of another. The necrotic parts gradually separate, and the patient may never have another attack, or in a year or two there is a recurrence.

"The severer form is a terrible malady, and may affect fingers and toes at once and with them sometimes the tip of the nose and ears. The pain is of great severity. Both feet may be swollen to the ankle with toes black. It may look as if both feet would become gangrenous, but as a rule the process subsides, and in a case of even greater severity only the tips of the toes are lost. A severe attack of this sort may last three or four months, when the patient recovers with the loss of two or three fingers or toes, a snip off the edge of both ears and a scar on the tip of the nose. Attacks of this severity may occur year by year, and there are terrible instances in which the patients have lost both hands and feet."

For years there has been a feeling among some clinicians that syphilis is responsible for certain cases that show symptoms that are almost absolutely characteristic of Raynaud's disease. I have had one apparently typical mild case where all of the lesions promptly subsided after the administration of arsphenamine. Lisser states that he can not feel that the definite proof has been advanced that Raynaud's disease may be due to syphilis, although there is a mass of evidence that makes this view extremely suggestive. He says that there are three possibilities, one, that there may be a definite syphilitic lesion of blood vessels or of the nerve supply to such vessels, two, that the symptom-complex may be due to syphilitic toxins, and three, that the bodily resistance may be so lowered by syphilis that the individual may be more susceptible to Raynaud's disease.

Cases of acquired syphilis which show the Raynaud's symptoms complex have been reported by Raynaud,[95] Defrance,[96] Liston,[97] Morgan,[98] Amann,[99] Castellino and Cardi,[100] Elsenberg,[101] Fordyce,[102] Giovanni,[103] Germer,[104] Morton,[105] Puzey,[106] Riva,[107] Tounton,[108] Balzer and Fouquet,[109] Lustgarten,[110] Cassirer,[111] Phelps,[112] Schuster,[113] Gaucher,[114] Gougerot and Meaux,[115] Saint Mare,[116] and Semon.[117] Cases where congenital syphilitics developed the trouble will be found mentioned in the chapter on Congenital Syphilis.

Aneurysm

According to Osler[118] a number of the very early writers upon aneurysm recognized that it was frequently associated with syphilis. Ambroïse Paré, Lancisi, in his admirable *De Aneurismatibus,* Romae, 1728, and Morgagni in his *De Sedibus,* all mentioned this fact. Other writers who have emphasized the relationship of thoracic aneurysm to syphilis are Welch,[119] Malmsten, Hampeln, Heller,[120] Etiénne, Pansini, Döhle,[121] and others. Since the advent of the Wassermann reaction it has been generally recognized that a positive reaction is found in from 50 to 85 per cent of all aneurysm cases, as the figures collected by Pearce,[122] as well as the publications of Anders,[123] Longcope,[124] and many others, including ourselves, show.

There has been a general belief on the part of many of the medical profession that aneurysm, excluding those produced by wounds, is always of syphilitic origin. That syphilis is the great cause is now universally conceded, but that there are other causes is made manifest by a careful reading of the literature. Other acute infections may occasionally cause aneurysm. Osler[118] quotes a case of Renon's where acute rheumatic fever was responsible. Haythorn[125] has reported a case due to tuberculosis, and has collected others from the literature. Mycotic aneurysms due to infected emboli have been reported. Osler[126] states that in horses aneurysms may result from the growth in vessels of the Strongylus armatus. Further references may be found in the new work of Barker.[127] As pointed out in the section on syphilitic arteritis a mesarteritis is undoubtedly the starting point of syphilitic aneurysms, and the vast majority

of all aneurysms start in this way. Probably about 30 per cent of all cases of arteritis result in aneurysm.

There is a rather general tendency to assume that aneurysm almost invariably occurs in the thoracic aorta, but that this is by no means always so is proved by the figures of Crisp:

Pulmonary artery	2
Thoracic aorta	125
Abdominal aorta	59
Common iliac	2
External iliac	9
Gluteal iliac	2
Femoral iliac	66
Popliteal	137
Posterior tibial	2
Innominate	20
Carotids	25
Intracranial	7
Temporal	1
Ophthalmic	1
Subclavian	23
Axillary	18
Suprascapular	1
Brachial	1

However, that these figures are not strictly accurate in the light of present knowledge is shown by the fact that aneurysms of the cerebral vessels are now known to be extremely common. Moreover the fact that a great many aneurysms are now being recognized, thanks to the x-ray, would undoubtedly increase the proportion of the thoracic ones highly.

Inasmuch as the thoracic aneurysm is the one that most concerns syphilographers, and inasmuch as it should be diagnosed at an early period, I shall confine the description of the clinical course to this one variety. There are two common types, the diffuse, which is due to a general dilatation of the walls of the aorta, and the circumscribed, which is due to a giving away of the wall in one portion only. Aneurysms are most common in the ascending aorta and in the arch. In the former type, the physical signs are usually rather more pronounced than are the symptoms. A pulsation may be seen in the second or third interspaces, and this may be palpated as well, together with

a thrill and diastolic shock. At times percussion will outline the mass. An aortic systolic murmur is common.

In aneurysms of the transverse and descending portions of the aorta symptoms are more prominent than are physical signs, due to the structures pressed upon. Aneurysm should at least be suspected in every patient who complains of pain in the chest, intercostal neuralgia, oppression, difficulty in swallowing, or a continued cough. For early diagnosis the fluoroscope is far the surest means. Special reference will be made to this point in the later chapter upon Diagnosis. An excellent discussion as to the diagnosis and bibliography is to be found in Barker's work. Broadbent's[128] description is still unexcelled.

In regards to the treatment of aneurysm there are two points to be emphasized, in the first place the local damage to the vessel must be treated as outlined in the various works upon medicine. In the second place the syphilis should never be neglected, for while the aneurysm can not be cured, at least in the majority of instances, the patient can be rendered much more comfortable. At times this may be distinctly dangerous, for a man may feel that he is well enough to resume active work, when such is not the case. Personally I give arsphenamine in about 0.4 gm. doses, employing a sufficient number of injections to render the Wassermann negative. It is amazing how much more comfortable the patients can be made. This would seem to indicate that the pain is frequently due to the syphilitic process rather than to pressure. Mercury should always follow up the arsphenamine. The more I see of antisyphilitic treatment in aneurysms the more enthusiastic I become over the temporary relief.

Arteriosclerosis and Hypertension

At the onset it should be distinctly understood that arteriosclerosis and hypertension are by no means synonymous terms. Hewlett[129] very clearly emphasizes this point in his recent book. Either may, and frequently does, exist without the other.

As regards the etiology of arteriosclerosis, there is still much dispute. Barker[130] states: "The process has been supposed to

be due chiefly to chronic intoxications (alcohol, lead, gout, diabetes, syphilis and other infectious diseases, nephritis, adrenal hypertrophy, digestive disturbances). As one's clinical experience grows, however, one is more and more impressed with the importance of the quality of the tubing a person starts with, and the character of the endocrine glands." There is, of course, a very distinct impression that a rise in blood pressure is usually a compensatory process, frequently due to disease of the kidneys, and more occasionally to the demands of the brain.

The literature concerning the importance of syphilis in these conditions is scanty. Cautley[131] and Albutt[132] feel that syphilis plays a very little part in the production of either arteriosclerosis or hypertension, while Stoll[133] takes the opposite view stating: "Syphilis is the underlying or basic factor in a much higher percentage of hypertensive cases than has hitherto been realized. Of fifty individuals studied, over 90 per cent gave either a positive Wassermann or luetin test, or were known to have had lues, or had children with hereditary syphilis. It would seem that hypertensive disease is one of the most common—possibly the most frequent—of the so-called 'late' manifestations of hereditary syphilis." In going over Stoll's figures, however, it is important to note that he makes no mention of the fact that potassium iodide is now known to sensitize a nonsyphilitic individual so that he will give a positive luetin test. Further he accepts a positive luetin as an adequate diagnosis of syphilis. This point will be discussed more fully in the chapter upon Diagnosis. Personally I feel that renal hypertensive cases in the young, where there is not a previous history of severe malaria, pneumonia, or of scarlet fever, are frequently due to syphilis, and I find that my medical confreres at the Freedmen's Hospital take the same view. Several times, in administering antisyphilitic treatment to an individual, who showed a marked hypertension, it has been found that the pressure would fall, and stay down, although this is by no means the common experience as Levison[134] has pointed out.

To sum up the whole situation: the question as to the etiologic importance of syphilis in either arteriosclerosis or hypertension

is still far from being a closed book. We must keep open minds on the whole question.

Syphilis of the Veins

The literature upon syphilitic phlebitis is extensive, although the disease is encountered none too frequently. It would seem that most of the cases that have been observed have been reported, as the bibliographies cited by Gaillard,[135] Hoffmann,[136] Janson,[137] Winternitz[138] and Friboes[139] would seem to prove.

Hoffmann's article is still the classic. Hoffmann distinguished three forms of venous syphilis, the diffuse thickening of a vein, the nodose thickening and the erythema nodosum syphiliticum. Hutchinson[140] has described a fourth form of periphlebitis. In the first form, which may occur either during early or late syphilis, a vein may be involved for practically its whole extent, or for only a portion of its length. Either a deep or a superficial vein may be affected, and the swelling may be either uniform, or more frequently irregular in different portions. There are always present the characteristics of inflammation, namely swelling, heat and pain. Pathologically both the venous and perivenous structures are involved by a diffuse syphilitic process. The second type is similar; the whole vein is not affected, only various portions of it. In the third type the eruption simulates erythema nodosum, the nodules usually lasting but a few days or weeks. As regards the variety described by Hutchinson that author states: "There is a curious form of periphlebitis due to syphilis which is often very chronic in its course, and produces very peculiar changes. It is attended by great thickening around distended and convoluted veins, which become matted together in a cake-like mass, and adherent to the skin. Sometimes suppuration occurs and portions of cellular tissue slough, producing characteristic sores, but in other cases the condition may last, in a state possibly of partial cure by specifics, for many years. It always tends to spread. Slight forms of syphilitic periphlebitis are not uncommon and are usually seen in the legs."

Late articles describing the condition are those of Philipson,[141] Strandberg[142] and Achard and Demanche.[143]

Blood Changes in Syphilis

Red Blood Cells.—Zeisler[144] has written an excellent account of the early work done upon the red blood cells, and has reviewed the literature to date. According to him the first work upon the erythrocytes was done by Grassi,[145] a pharmacist in the Hotel Dieu, under the instigation of Ricord. Later work has been done by Lezius,[146] Andrewes,[147] Stoutkovenoff,[148] Emerson,[149] Konried,[150] Newmann and Konried,[151] Gaillard,[152] and Cabot.[153] In general it may be said that all of the accounts agree, for the general opinion is that in the vast majority of instances there is but little change in the number of red blood corpuscles early in the course of the disease, although women may show a drop of 20 to 25 per cent. In late syphilis there may be an extreme anemia, a reduction both in the cells and the hemoglobin, the color index usually being low. Müller,[154] Weicksel[155] and others have reported cases of pernicious anemia as being due to syphilis. Referring to this point Emerson states: "In hereditary and tertiary lues the red blood cells are seriously affected, in number, size and color. Megaloblasts are common. The blood picture, especially of the long-standing cases with much scarring of the organs and sclerotic bone marrow may resemble primary pernicious anemia."

Hemoglobin.—It is generally agreed by the above-mentioned writers that early in the course of syphilis, before the rash has appeared, there is a marked reduction in the amount of hemoglobin. In the European clinics great stress was formerly placed on the value of this fact, especially in diagnosing chancres in women. Quite frequently if a large inunction or injection of mercury be given just before the development of the rash there is an immediate drop of from 10 to 20 per cent in the hemoglobin, and then a rise to normal. Justus has taken advantage of this fact to develop a test which he claimed as specific for syphilis. This test has been investigated by Brown and Dale,[156] Jones,[157] Christian and Foerster[158] and others, and they all claim that it is not of the value that Justus thought, inasmuch as it is not invariably present, and inasmuch as other conditions may give the same result. Justus[159] has answered his critics and still claims that the test is specific. As a matter of fact

the later developments in laboratory work, namely, the finding of the causal organism and the Wassermann reaction have made this test superfluous. In late syphilis there is often a marked reduction in hemoglobin along with the secondary anemia. In the early stages the anemia is often of the chlorotic type, but not so in the late stages.

Leucocytes.—The leucocytes in syphilis have been studied by Rille,[160] Peter,[161] Jelenew,[162] Hauck,[163] Bieganski,[164] Watabiki,[165] Emerson and Cabot. However, I[166] have made a most complete study of the subject and have reached the following conclusions:

In a series of 125 syphilitic cases, embracing 175 differential counts, all done by the same person and with the same technic, and in a control series of cases there were the following results:

1. In normal persons the average total count is about 7,500, the neutrophile count 55 per cent and the lymphocyte count 33 per cent.

2. In the untreated secondary cases there is a slight leucocytosis, an occasional case showing as many as 20,000 white blood cells. The neutrophiles are absolutely and relatively increased. The percentage of eosinophiles is higher at this time than in control cases or in cases of late lues. Treatment causes a slight drop in the total count, with a slight actual and marked relative increase in the lymphocytes.

3. Under treatment a secondary case may show a lymphocytosis as high as 65 per cent, a condition that may persist for many months, or that may tend to approach normal in from three to five months, even though treatment is continued.

4. Cases of tertiary lues very rarely show an increase in leucocytes. The differential count in untreated cases is usually not far from normal. Myelocytes are very rarely found, even with moderate anemia. Treatment usually but not invariably causes a rise in both the relative and actual number of lymphocytes.

5. The cases with a large papular eruption, all in this series occurring in negroes, show a higher percentage of lymphocytes than do the other types of secondary eruption. The average is 42 per cent.

6. In cases of secondary syphilis, negroes show a higher lymphocytosis, 35 per cent, than do whites, 26 per cent. In the late cases there is not so marked a difference.

7. Males show a slightly greater increase in the total count than do females, females show a higher lymphocyte count than do males.

8. Age makes very little difference in the count. The very young tend to have a high neutrophile and a relatively low lymphocyte count.

9. Marked glandular enlargement does not mean a high lymphocytosis, in fact there seems to be very little relationship between glandular involvement and the number of small mononuclears in the circulation blood.

10. Severe cases of secondary syphilis show a higher total count and a higher actual and relative neutrophile count than do the milder cases.

11. All cases of secondary syphilis that did badly under treatment, showed before treatment was begun, a high neutrophile and a low lymphocyte count; all cases that showed a low neutrophile and high lymphocyte count did well.

12. Cases of late hereditary syphilis do not necessarily show a high lymphocyte count.

13. Eosinophilia, in a case of skin eruption, speaks against syphilis.

One of the most interesting features of this study was the possible prognostic value of a differential count. The data on this point were as follows:

Eight cases of early untreated syphilis, showing secondary manifestations, were followed for several years; all did well, responding kindly to treatment and not suffering relapses when it was temporarily discontinued.

The average count in these cases was:

W. B. C.	*Polys.*	*Eosins.*	*Large monos.*	*Lymphocy.*	*Trans.*	*Mast cells.*
12500	53.9	3.5	0.9	37.4	3.2	0.9

Two of these cases showed low lymphocyte counts, about 20 per cent each, while the remaining cases showed high lymphocyte counts.

Six cases of secondary syphilis did badly under mercury by

mouth, inunction or injection, and three of them failed to clear up under arsphenamine.

The average count before treatment was started was:

W. B. C.	*Polys.*	*Eosins.*	*Large monos.*	*Lymphocy.*	*Trans.*	*Mast cells.*
13900	73.4	3.9	1.0	18.2	2.7	0.3

With one exception all of these cases were followed for at least two years and several other counts made: the average of these counts, made several months after treatment was begun, and regularly kept up, was:

W. B. C.	*Polys.*	*Eosins.*	*Large monos.*	*Lymphocy.*	*Trans.*	*Mast cells.*
10000	51.3	2.9	0.4	41.4	3.4	0.4

It is evident that a deficiency in lymphocytes can not be a factor in the intractable course of the disease, for these cases continued to do badly after the lymphocyte count had risen to above normal.

In tertiary syphilis the same rule seemed to hold.

Nanta[167] has suggested that perhaps some cases of leukemia may be due to syphilis. However there is nothing in the literature to support this.

Syphilis of the Spleen

The following account of early syphilis of the spleen is taken entirely from Wile's[168] recent article. The first account of syphilis of the spleen during secondary lues was that of Biermer[169] in 1862. In 1874 Weil[170] drew particular attention to this phenomenon. Other accounts are those of Gold,[171] Columbini,[172] Bruhns,[173] Wewer,[174] Haslund,[175] Nolte,[176] Avanzini[177] and Schuchter.[178] Wile examined one hundred cases of primary and of secondary syphilis and found splenic enlargement in thirty-six. The spleen was hard and firm in seventeen cases, soft in three and tender in six. The majority of the cases showed marked impairment of the general health. The enlargement may occur before the eruption appears. The enlargement tends to disappear under treatment, but like other hypertrophies of lymphoid tissue may persist for a considerable space of time.

Osler[179] states that four types of splenic lesions may be found in late syphilis. Gummata are the most common; they have

been well described by Wilks.[180] They may be either single or multiple, large or small. They are often associated with gummata of the liver. Perisplenitis may exist in the form of a thickened capsule. Cicatrices may result from old gummata, and the spleen resemble an old syphilitic liver, in that scars and depressions are marked. Amyloid changes may occur in long-standing cases, especially where the bones or liver have been seriously affected. They may be confined to the Malpighian bodies, or the process may be diffuse. In some instances leucemia may be simulated, both by the physical and by the blood findings.

Clark[181] and Neuberg[182] have both reported instances where splenic anemia was closely simulated, and it is more than probable that certain cases of Banti's disease are due to syphilis, either congenital or acquired.

Syphilis of the Lymph Nodes

As is well known, the lymph nodes in a patient suffering from early syphilis are frequently enlarged, and by some men much stress has been put upon the diagnostic value of this point, while by others this value has been decried. As already stated, Neisser has found that treponemata can be demonstrated in the neighboring glands even before the chancre has become manifest. Friedländer[183] has written the best article upon the clinical value of lymph gland examination in syphilis. He finds that unilateral enlargement has but little significance, but that the bilateral enlargement of certain groups is of considerable importance. For instance, he found the epitrochlear glands an average of 77 per cent enlarged in syphilis, and but 27½ per cent in nonsyphilitic conditions, of the occipital 82 per cent in luetics and 45 per cent in other patients, and of posterior cervical 84 per cent in syphilitics and 47 per cent in nonsyphilitics. It is a well-known fact that in the negro race glandular enlargement is more frequent and more pronounced than in whites. In late syphilis glandular enlargement is not so constant as in the earlier stages of the disease. Two points should be especially noted, first that universal glandular enlargement is very suggestive of syphilis, and second that enlargement of the submammary lymph nodes is also extremely suggestive.

Late in syphilis gummous changes in the glands are occasionally met with, much more frequently in the negro than in the white. These lymphomata have been described by Montgomery and Culver,[184] Fasal,[185] Wile,[186] Nanta,[187] Potier,[188] Cahen,[189] Lustgarten,[190] Dalbancos,[191] Cornil,[192] Lowenbach[193] and others. I have now seen twelve cases of lymph gland gummata, all but one of the cervical region. All but one occurred in negroes. There may be one gland or a group of enlarged

Fig. 102.—While gummata of the lymph nodes are rare in the white race, they are much more frequent in the colored. In this instance the submammary lymph node was affected. (Collection of Dr. T. Caspar Gilchrist.)

glands, which may remain hard or which may soften and break down. Several were operated upon for tuberculosis, so that at the Freedmen's Hospital all cases of cervical adenitis now have a blood test done. Young patients are most frequently affected, all of my cases being between the age of twenty and thirty-five. Males and females were not affected alike, there being but four women in the series. Wile states that glands of the groin are not infrequently attacked, and less frequently the axillary. Virchow[194] states that there may be a marked anemia and at

times a marked leucocytosis. In my series of cases no characteristic blood changes could be demonstrated.

Cornil, Lowenbach and Fasal concur in the opinion that the histopathologic picture is not characteristic of lues, but that it may resemble either an endothelioma or a large-celled sarcoma.

In my experience the cases require considerable treatment before any marked amount of improvement is noted.

Mikulicz's Disease

Theodoresco[195] believes that syphilis is the most common cause of Mikulicz's disease. He reports a typical case in a woman who gave a positive Wassermann, and who was speedily cured by injections of calomel.

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CHAPTER XIV

SYPHILIS OF THE BONES, JOINTS, MUSCLES, TENDONS, AND BURSÆ

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Syphilis of the Bones

Although syphilis of the bones has been recognized for a long time, Jean de Vigo, writing of it in 1514 and Fallopia[1] in 1555, and although it has been described by Verneuil, Astruc,[2] Pittit and denied by Hunter,[3] yet it is only within recent years that we have begun to appreciate the fact that syphilitic affections of bone play one of the most important roles in the drama of syphilis. The discovery of the cause of syphilis, the Treponema pallidum and the diagnostic test of Wassermann have enabled us to prove that many of the more vague and hitherto undiagnosed cases of bone disease are syphilitic in their nature.

The pathology of bone syphilis was recognized and very well described in the middle of the last century by such observers as Ricord in 1851,[4] who reported several cases of gummata of the long bones, and Virchow in 1862, who wrote on gummatous osteomyelitis of the tibia with peripheral hyperostosis and alteration of the marrow. Since these pathologic exhibitions, the literature has abounded in studies by such observers as Cornil, Jullien, Zeissl,[5] Poncet, Rolet, Neumann, Fournier,[6] and more recently by Gangolphe[7] of the Lyons School, who made an exhaustive study.

In the last decade since new methods of diagnosis have come into vogue, we have many new phases of the subject presented; for instance, syphilis of the vertebral column has recently been described by Ramsey Hunt,[8] of New York, Whitney and Baldwin,[9] of San Francisco, and Ziesche.[10]

Frequency.—Within the last few years much has been written as to the occurrence of bone involvement, especially in connection with spinal involvement and the arthropathies; and yet Jullien, in 1879, stated that 27 per cent of syphilitics have bone lesions. It is of interest to note that in his table of percentages, the occurrence was somewhat affected by treatment; for instance, where patients received mercurial treatment from the very start, there was only 21 per cent with osseous lesions. Where treatment was begun at the beginning of the secondary stage, the percentage was raised to 25. Where the treatment was started early, the average onset of bone lesions was four years, whereas in the untreated cases, or those with treatment started in the secondary stage, the average of onset was three years and nine months. In more recent articles Whitney and Baldwin, who studied a series of 100 consecutive cases of syphilis treated in the hospital, where the opportunity for observation was greatly enhanced, state that 68 had spinal abnormalities of some kind. They describe two types of involvement, (a) infectious; (b) toxic. Under *a*, they describe (1) gummous lesions in the vertebral bodies, (2) synovitis without destruction.

It will be seen from these widely different sets of figures that syphilis is at least a condition to be considered in all bone affections, and when we consider that syphilis is primarily a blood infection, and that bones are most important hemopoietic organs, this is not to be wondered at. When our observations have become more thorough, even a higher percentage will be recognized. The latter statement is well borne out by the recent work of O'Reilly[11] at the Washington University Hospital at St. Louis where a routine Wassermann is made in all chronic bone and joint cases to determine the absence or presence of syphilis.

Time of Onset.—Spillmann,[12] in his thesis of 1909 on Syphilis Osseuse before the faculty at Nancy, states that bones may be attacked from the very start, a few months or even weeks after the appearance of the chancre, even before the skin lesions make their appearance. As a rule, demonstrable bone lesions occur from five to thirty years after the first accident. From this statement, and our appreciation of the early involvement of the hemopoietic tissues, we may appreciate the fact that bone lesions

of some character are possible from the beginning of the disease throughout the entire period of infection.

Fournier in 655 observations shows an almost perfect parallelism between tertiary bone lesions and general tertiarism in the following table:

Time	*General Lesions per cent*	*Bone Lesions per cent*
For the first 10 years	70.	73.8
" " next " "	22.3	18.
" " " " "	5.	5.8
" " " " "	1.	1.5
Beyond 50 "	0.28	0.5

In a further statement, he says that bone lesions are almost as frequent in the first year of infection as in the seventh, but most common in the third year. This is likewise true of definitely demonstrable general tertiary lesions. Our better understanding of the general subject of bone involvement leads us to believe that we have a very much earlier onset than these figures would give us to understand; for instance, in the so-called rheumatic bone pains occurring in the early stages of the infection, it is only fair to assume that there is a definite involvement of the bone marrow, either the central bone marrow or the subperiosteal bone marrow, which may be the cause of such pains, and that the swelling which would go with such an acute infection causes pressure symptoms. It would be very difficult to prove any set of figures along these lines because of the impossibility of testing our clinical observations by pathologic study; however, it is only fair to assume that there must be some pathologic change for the production of these very definite symptoms.

Much has been written of the osteocopic night pains, and we are firmly of the belief that syphilis is one etiologic factor in this very important clinical phenomenon.

Localization.—For many years, nodes on the crest of the tibia have always made us suspect syphilis, but without impressing us with the importance of such a phenomenon in relation to general or localized bone syphilis. A few of the percentages taken from the literature are of interest in this respect. Gangolphe and Perret, in 49 cases of bone syphilis, gave the follow-

ing localization: femur 26, humerus 28, tibia 18, radius 10, sternum 3, clavicle 16, patella 1, radius 3, forearm 2, scapula 4.

Jullien in 64 cases, gave the following: nose 19, tibia 15, palate 15, sternum 5, clavicle 4, maxillary 4, frontal 1, parietal 1, vertebra 1, scapula 1, forearm 1, knee-cap 1.

Fournier, on the other hand, showed that of all of the involvements, the tibia was affected in 26.3 per cent, nasal palatal skeleton in 25 per cent, and the cranium in 19 per cent.

From these figures, it will be seen that the tibia plays a very important role, and that the bones of the nose and head are also frequently involved. Fournier unquestionably included the congenital cases in his list.

Schulmann[13] of New York reported two very interesting cases of involvement of the sternum, symptomatically simulating cardiac lesions, and it was only by the most careful observation that the bone changes were made out.

The most recent writings go to show that the vertebral column is much more frequently involved than was heretofore believed possible. Hunt, in reporting 100 cases, found that the cervical region was the point of election, and that the frequency diminishes as we descend the spine. In Whitney and Baldwin's series of 100 consecutive syphilitics examined, they found that only 26 had normal spines. In six cases, there was a doubt; 68 had definite abnormalities.

Ziesche reviewed 86 cases of syphilis of the vertebræ and found that the cervical vertebræ were involved in 61. He also states that in 41 per cent, only one vertebra was affected, 2 in 28 per cent and 4 vertebræ affected in 5 per cent. This latter statement, if verified in any great collection of cases, will be of the very greatest importance in differentiating syphilitic spondylitis from tuberculosis.

Under the general subject of localization, Fordyce's[14] statement may be quoted: "The relation of trauma to the localization of specific lesions has been so well appreciated by the medical profession that it is given a prominent place as an etiologic factor." From this, we must appreciate that the more subject the skeleton is to trauma, the more frequently will we find bone involvement.

Etiology and Pathology.—The pathology of bone syphilis is the same as that of syphilis of any other organ with special consideration for the anatomic structure of the bones. Bones consist of inorganic material, chiefly phosphate of lime, permeated throughout with connective tissue and fat, the latter more abundant at the central portion and within the spongy parts, and richly supplied with blood vessels.

As has been said before, the predilection of the Treponema pallidum for the hemopoietic organs makes it very easy to understand why osseous tissue as the greatest of hemopoietic organs becomes so frequently attacked. There is no tissue so abundantly supplied with lymphatics as the bones, both in the medullary and subperiosteal marrow. "It has been demonstrated by Neisser that the spleen and bone marrow of inoculated monkeys contain virus early in the infection."

Levaditi[15] argues that the treponemata, even before the evolution of the primary lesion, may penetrate the hemopoietic organs, and that they act like true antigens and their products of secretion stimulate formation of antibodies. These different quotations are given to prove the early involvement of these tissues.

Inflammatory Lesions.—Fordyce describes the manner of vascular involvement. He says that the pathologic process consists of arteritis or panarteritis with characteristic inflammatory infiltration. The syphilitic process is essentially a granuloma having its origin in the upper vascular lymph spaces.

There is no essential difference in the pathology of syphilitic lesions in the early stages, no matter where they occur. In bone syphilis, these changes take place not only in the marrow, but in the Haversian canals through which the blood supply to the bony tissue itself takes place. This vascular involvement may attack either the subperiosteal or the center marrow. In the former case, a periostitis would be the result, in the latter an osteomyelitis. Should the disease be stopped during this stage, little or no scar would remain. The process, however, may go on to an irritative condition producing bone formation; in the case of periosteal involvement producing an exostosis. Where this proliferative change is within the bony tissue, the result is an eburnation, that is, the Haversian canals become

filled up due to the stimulation of the osteophytes. There is sometimes a rarefaction of the bone about these vessels which produces a definite bone destruction. This may go on to a true necrosis with a liquefaction which may end in suppuration. It would be difficult to understand cases of suppuration unless there were a secondary infection.

A. Periostitis and Osteoperiostitis.—Periostitis is a swelling of the periosteum or subperiosteal marrow, and is caused by a true primary vascular change. This swelling interferes with the many little nerve filaments running from the periosteum to the bone, thus causing the pain characteristic of this form of disease. The osteoperiostitis is an extension of the disease into the bony tissue, that is the Haversian canals. These inflammatory processes may end by resolution, especially under treatment, or they may progress to a rarefying osteitis or to a proliferative osteitis, the latter causing an eburnation or formation of osteophytes or exostoses. Rarefying osteitis progresses by destroying the walls of the Haversian canals producing a spongy condition of the bone which may or may not be filled up by bone proliferation. If not, necrosis is the result. Suppurating periostitis is the result of a secondary infection involving the injured tissues.

B. Gummous Lesions.—Gumma is the typical lesion of the tertiary period, and is the end result of the proliferative changes of the inflammatory period, that is, as the inflammation advances and the fibrous elements become more dense and contracted, the blood supply to the center cells becomes gradually diminished. There is a degeneration of the central cells and finally a background of granular matter is the end result of this degeneration. As a result of this, the center of the tumor softens, and gradually caseates while the periphery preserves its normal appearance. In the bones gummata evolve as in any other tissue, and may be found wherever the inflammatory process previously described has existed. Gummata of the bone may be periosteal, subperiosteal, osseous, or osteomyelitic. The gummous destructive processes, as we might expect, are more extensive than the destruction accompanying the true inflammatory lesion.

This pathologic process takes place in any of the bone tissues, but the more spongy or less dense the bone tissue is and the better its blood supply, the more apt is it to become involved and

so in our localization, we find that bone involvement much more frequently takes place in the widened portions at the ends of the bones and in the bony tissues which are not so dense.

The gummous formation may affect all parts of bone structure. It may be circumscribed or diffuse. If confined to the dense bone or to the periosteal bone marrow it is spoken of as gummous osteoperiostitis; if confined to the bone marrow, as gummous osteomyelitis. There is also a microscopic difference according to the type of bone involved. For instance, when the flat bones such as are found in the cranium are affected, the process is a proliferation of tissue penetrating from the pericranium and a like process from the dura mater or the inner table of the bone so that the bone will be tunneled with small spiral galleries giving a worm-eaten appearance. This may go on to a more widely scattered process so that large portions of bone are destroyed, even up to three inches in diameter.

When the long bones are affected, the periosteum is much thickened as a result of the underlying inflammation and the periosteum becomes densely adherent, being difficult to detach from the underlying bone. The bone surface is frequently roughened due to the bone proliferation set up by the inflammatory process and this may form exostoses. The surface of the long bones may be covered with holes similar to those found in the flat bones above described (as a result of a gummous attack on the flat bones of the skull). These holes in a fresh specimen are found filled with gummous tissue. When dry, they give a sieve-like appearance. This destructive process may progress and destroy the walls of the Haversian canals. The surrounding bone may be rarefied and become brittle, or new bone formation may take place through the stimulated action of the osteophytes, producing an eburnation or exostosis. At times, necrosis sets in with production of a sequestrum, or there may be a destructive action with partial or complete disappearance of bone. The latter is especially noticeable in the cranium.

Lesions of Special Bones.—*Long Bones.*—The diaphysis is usually increased in size, the periosteum thickened and adherent. The increase may be localized or general, depending on the extent of the involvement forming either globular masses or a spindle-shaped tumefaction. The contour of the entire bone may be

changed, especially noticeable in the tibia, producing the so-called saber-shaped tibia, a frequent occurrence in congenital syphilis. At times large portions of bone are so involved and increased in size that the normal contour is very much changed. Observations of this character have been noted in the femur which has assumed the shape of a cudgel. The clavicle is another example where an entire bone may become two or three times its normal size.

Short Bones.—The phalanges are frequently perforated or parts may entirely disappear causing a shortening, or there may be typical periostitis with surface roughening.

Flat Bones.—As before stated, the cranium, especially the anterior vault, is frequently the seat of destructive processes, and there are numerous examples in the museums where large surface areas have been eaten away, or complete perforations have taken place as though produced by a bullet. The sieve-like formation is rather the common observation, the holes completely penetrating the skull. The bones of the face are a favorite seat of syphilitic destruction, especially the bones of the nose, producing the so-called saddle nose.

The Spinal Column.—There may be a simple inflammatory periostitis or gummous lesion. If a periostitis, it resembles periosteal thickenings due to other infectious agents. If a gummous lesion, it attacks any portion of the vertebra, but as a rule, the vertebral body is alone attacked. If the latter, the spindle-shaped portion of the bone is transformed into a soft yellowish detritus or even a purulent liquid. It may not proceed to this degree, rarefaction being the most noted change. Breaking down of the vertebral bodies under this condition due to the superincumbent weight is possible, such as is seen in the early or slowly developing tuberculous lesions. The more dense portions of the vertebra, the posterior arches, and the processes may also be attacked. The process may also extend to the intervertebral discs and the surrounding ligaments.

Clinical Study.—Spillman states that there are two never-failing signs of bone involvement: first, pain; second, tumefaction; and that there are two negative signs: first, absence of suppuration; second, absence of glandular enlargement corresponding to the lesion. In the very early cases, demonstrable bone

lesions are rare; as in cases in the pre-chancre period with osteocopic pains. Here nothing is to be seen or felt, and even a negative x-ray finding is usual. These are thought to be the cases of early bone marrow involvement. The pains vary but are often extensive and lancinating. They may come and go, almost always appearing at night and are a most important diagnostic sign of bone syphilis. They jump from one part of the body to another resembling so-called rheumatic pains. At this stage, there is no tenderness to pressure, and they are not associated with trauma. They disturb the rest of the individual greatly, and usually have a deteriorating effect on the general health by continual interference with rest. They may appear once or twice during the night, the favorite times being at eleven at night and again between one and two in the morning. One observer reports a patient who was able to stop the pains by making a light. Many theories have been suggested as to the cause of such pains such as the body becoming overheated by the bed clothes, or by the taking of the horizontal position, but none of these have been borne out by any series of observations. Another observer suggested that they might be due to special activity of the treponemata at this time, but this, likewise, is unconfirmed. The fact is, however, that osteocopic pains occur; especially at night; that they are excruciating and lancinating in character, and that little can be done to check them other than the employment of antisyphilitic treatment. They are most suggestive of syphilis, and when present, this disease should be suspected. There are other pains occurring late in bone syphilis, that is, in those cases where there is a demonstrable lesion. They are rarely commensurate with the lesion and do not shift from place to place. They may be superficial or deep seated, the patient frequently knowing that the pain is deep as though in the bone. They also may be lancinating or terebrating and they have a grave effect on the health of the patient. Zeissl who first described them suggested that they were due to the breaking away of the walls of the Haversian canals, but other observers believe that the whole process is one of increased tension from the pressure of the involved tissue, either in the central or periosteal marrow, or in the soft tissue filling the Haversian canals. In my observation, the absence of pain on pressure, or

from use in comparison to the extent of the lesion is always of the greatest help. Surely there is no chronic inflammatory process which can stand so much traumatism with so little disturbance.

Tumefaction.—The more superficial the bones, the more apt they are to be found involved. This may be due to the fact that they suffer traumatism more readily, leaving a more fertile field, or it may mean that the deep-seated bones are more difficult of examination. In the cases of periostitis, a spindle-shaped swelling is the rule, either localized, or involving a large part of the bone. Usually the radiographic findings show single or multiple periosteal thickenings. Often the entire bone is thickened, especially the cortical layer, if the disease is of long duration. Such is a true osteitis with proliferation of bone elements.

There is often a roughening of the surfaces of the bone which may present definite exostosis. If the condition is a gummous involvement, nodular areas may be made out, single or multiple, their consistency depending upon whether the gumma is firm or has undergone degeneration. Unless the overlying tissues have become involved, they remain normally clear and the local temperature is normal. If, however, a gumma has extended or has broken down and is suppurating, the surface shows signs of local irritation, that is a reddening or bluish reddening of the surface with a slight rise of temperature. Should such a process go on, ulceration is the result. If, however, regeneration takes place, a subcutaneous scar results which is rather peculiar to syphilitic lesions. On palpation, a star-like depression of dense fibrous tissue frequently below the normal surface of the bone can be made out. In the bones of the face, where ulceration takes place, complete destruction of bone may occur together with ulceration of the soft tissues, and communications between different fossæ of the face become prominent.

Adenopathy.—Spillman has said the absence of glandular enlargement is striking. Any glandular enlargement is due only to the general infection and not to a special involvement of the parts drained. This is due, no doubt, to the type of the disease being a stimulating change in the vascular system in a true suppurative inflammation with production of toxemias.

Clinical Aspect in Relation to Special Bones.—The bones most

frequently involved are the deep cranium, sternum, and clavicles. The curve of the top is often thickened, roughened, or even nodular according to the stage of the involvement. In the early cases a regular spindle-shaped swelling may be made out. There is usually some tenderness or puffiness of the overlying tissues, but no reddening, and little, if any, increase in local temperature. On careful palpation, one can usually find a small area of tenderness, but unless the examination is most carefully made, this may be overlooked. As the disease progresses, the swollen area becomes harder, which is probably due to the formation of subperiosteal bone or exostoses. At times involvement is so extensive that in the long bones a large portion of the bone is diseased and the whole shaft increased in size.

When gummous formation takes place, there is a softer sensation to palpation which may resolve into harder areas by the laying down of new bone. Around such areas there is always an edge of hard bone as in syphilis of the cranium. If resolution does not take place, the process goes on to softening and ulceration and where a sequestrum is formed, healing can not take place until the dead bone has been evacuated. This process is true of all superficial lesions and is especially true of the cranial lesions which are so numerous in the early stages.

Such early lesions may occur from four to six weeks after the appearance of the chancre and usually within the first four months. The favorite bone for syphilitic involvement is the clavicle which is often found thickened throughout its entire extent.

A young man was sent to one of us (J. D.) for symptoms referred to the shoulder joint. There was a dull ache in the general area of the shoulder and in the region of the acromioclavicular junction, somewhat simulating subacromial bursitis. On examination the entire clavicle was found to be enlarged with a suspicious thickening of the acromion process. There was no redness or local heat, but there was slight tenderness over the entire clavicle. The x-ray examination verified the clinical finding and a Wassermann reaction cleared up the diagnosis. Resolution took place under antisyphilitic treatment.

The sternoclavicular junction is also a favorite seat of the disease. A number of observers have called attention to sternum cases. Two very striking examples were reported by Schulman

of New York. In both instances, the patients complained of heart pain. Careful examination in each instance disclosed a small area of exquisite tenderness over the sternum. In each, therapeutic measures gave immediate relief of the pain and finally a cure. The conditions were gummata of the under surface of the sternum. These gummata of the sternum may also have the aspect of tumors with softer center and hard bony

Fig. 103.—Syphilitic swelling of the sternoclavicular articulation is common.

border. The characteristic feature of the sternum lesions is that they may occasion grave disturbances such as acute precordial pains, circulatory interference, shortness of breath, or pain simulating angina pectoris.

Bradrick called attention to substernal sensitiveness in the diagnosis of syphilis and Mauriac to the sternocostal neuralgia, accompanied by shortness of breath and precordial pains, in the early forms of syphilis.

Syphilitic dactylitis is of special interest because the ease of observation is important in suggesting a diagnosis. Periostitis is the more frequent type, while necrosis of the bones as a re-

Fig. 104.—Dactylitis may occur in acquired syphilis.

Fig. 105.—This shows another view of the same hand shown in Fig. 104.

sult of a gummatous condition is of rare occurrence. Portions of the bone may be destroyed, giving much the same x-ray appearance as is seen in chronic gout, that is a punched out area

Fig. 106.—In the same case shown in the two preceding figures the phalanges show considerable destruction of bone. (Roentgenogram by Dr. Walter Van Sweringen.)

in the shaft of the bone. Large portions of the shaft may entirely disappear and a shortening of the extremities results.

The most recent contribution to bone syphilis is the observation

of vertebral involvement though it was recognized by Fournier in 1881 and in the writings of Froelick, Feltgen, Joachimsthal, who wrote extensively from 1902 to 1904.

More recently Ramsey Hunt of New York reviewed the literature and found that out of 100 cases reported, the cervical region was by far the point of choice and that the frequency diminishes as one goes down the spine. The symptomatology of syphilis of the spine does not differ essentially from that of other affections of the spine, and consists especially of pain, tenderness, rigidity, and deformity. When the vertebral body is destroyed, the symptoms are not unlike those of Pott's disease, but the kyphosis which is so characteristic of Pott's disease is comparatively rare. This is due to the much less extensive destruction of vertebral bodies in syphilis. One observer states that in syphilis of the spine, one vertebra only was involved in 40 per cent of the cases. The attitudes assumed in spinal syphilis are not unlike those of true Pott's disease, that is, those attitudes due to a stiffness of the spine.

All bone pains are persistent and about 25 per cent of the patients have neural complications, such as anesthetic formication and motor disturbances, the greater portion of which, he states, are due to the extension of the disease into the cord or a compression myelitis. Abscess is rare. The x-ray examination of the cervical cases is of very little use, but in involvement of the lower portion of the spine may be very helpful.

It is stated that one vertebra only is involved in 40 per cent of all of the cases, that is, in the cases of actual bone destruction. This will be seen later to be of interest in the differentiation of tuberculous disease. The disease may be sudden, simulating an acute process, or it may develop gradually and may run an exceedingly chronic and protracted course.

In the observations of Whitney and Baldwin, who found a very high percentage of spinal involvement in 100 consecutive syphilitics, there is no statement as to the number of those with bone changes, most of their cases representing the so-called synovitis stage which will be taken up under the head of arthropathies. Wile reported a most interesting observation based upon the study of 165 cases of syphilis treated in a hospital where minute and complete examination was made with special reference

to the osseous system. He found that 36 per cent had bone involvement, that 60 per cent of these had other constitutional disturbances, 30 per cent of which were of a serious nature, such as anemia, debility, and loss of weight. He states that there is an inverse ratio between bone involvement and that of the nervous system. This statement is of particular interest in connection with the recent work of Reasoner upon strains of the treponema which will be noted elsewhere in this volume under the head of pathology.

Complications.—The most frequent condition complicating bone syphilis is an extension into the surrounding tissues; for instance, in the vertebral cases, nerve pressure symptoms at the roots as they pass out of the spinal canal or a direct involvement of the cord or meninges. Other instances of nerve involvement from extension are seen especially about the head where paralysis of the nerves controlling the muscles of the eye and ear are of not uncommon occurrence.

Fractures as a result of bone destruction are frequently seen and are so frequent as to arouse always in such cases the suspicion of syphilis. Within the last year, Groover of Washington has seen two cases of multiple spontaneous syphilitic fractures of the metatarsals, both of which were verified by the Wassermann reaction. The rarefaction that takes place accompanying bone involvement frequently allows fractures to occur during the ordinary routine of life which are not associated with any special trauma.

Diagnosis.—In some cases a diagnosis is easy, in others difficult and it may take all the means we have at our command to establish the true nature of the condition.

When we find a painful area in a bone, we first have to determine whether or not trauma has played any part in its production, but we must not be satisfied with thinking the lesion is necessarily solely traumatic as trauma plays such an important role in the production of a favorable soil for the development of bone syphilis. In the early periostitis cases, this may be a very difficult point to decide, especially if the lesion has been present over any considerable length of time. Whenever in doubt a serum test should always be made, even though no history is obtainable. In all cases, a careful resumé of the history and

especially of the antecedents should be made. The clinical signs are of the greatest importance. Spontaneous pain with nocturnal exacerbations, habitual absence of suppuration and glandular enlargements, normal skin, no increase in local temperature, and, as a rule, good general condition are important. Even in cases with a negative history and blood test, a therapeutic test is often diagnostic. I mean by this, a diminution or complete relief of the signs and symptoms upon administration of antisyphilitic medication. X-ray examination is of the greatest help.

Bone changes due to chronic infectious processes, such as are seen in the old nonsuppurating osteomyelitis cases, are difficult to differentiate from malignant bone involvement. Both cause great pain, nocturnal in character; both cause rarefaction; the latter is probably more rapid in its development. In new growth the condition is often more general, that is, more bones are involved. A careful examination will often reveal a primary growth elsewhere in the body. The therapeutic test here is also of the greatest value. In syphilis the pain is almost immediately relieved by antisyphilitic measures; in new growth, nothing seems to avail.

In the case of exostosis, the exostosis of hypertrophic arthritis and infectious arthritis as well as the atrophic cases must be taken into consideration.

Further information may be secured from the writings of Power,[16] Waldeyer,[17] Pitt,[18] Jasinski,[19] Wiggs,[20] Wholey,[21] Taylor,[22] Ashurst,[23] Skillern,[24, 25] Sachs,[26] Mauriac,[27] Chiari,[28] Ware,[29] Armour,[30] Axhausen,[31] Gregory and Karpas,[32] Peritz[33] and Tubby.[34]

Syphilis of the Joints

History.—The early literature is much more indefinite regarding arthritic than osseous syphilitic affections. However, that it was far from unknown, or at least unsuspected, is evidenced by the early writings quoted by Gouriantz in a recent thesis. Gouriantz calls attention to the fact that Pierre Martyr in writing to his friend Arias Barbosa in 1488 definitely mentioned joint lesions as associated with syphilis. Unfortunately we have been unable to confirm this date, which would certainly place the advent of syphilis in Europe before the return of the sailors of

Columbus, hence we feel that this reference must be taken *cum grano salis.* However, a number of other references are beyond criticism. For instance, Villabos in 1498, Fracastor in 1546, Ambroïse Paré in 1561, Levinus Lemnius in the same year, Della Croce in 1583, all described syphilitic joint pains. There the matter rested until 1837 when John Hunter denied the possibility of arthritic involvement in syphilis, while Chornel (a poet) and Babington insisted upon its occurrence, while Ricord was undecided. In 1853 Richet definitely described gummata of the articulations and also an early synovitis. In 1863 Lancereaux saw the first autopsy where articular syphilis existed. About the same time Fournier described a number of types of joint syphilis. Since this time many cases have been described and many articles upon the subject have been written, two of the most complete being the theses of Gouriantz[35] and Pillon.[36]

Frequency.—Even yet it is a bit uncertain as to just how frequent this form of syphilis is. Every clinician knows that a high percentage of all syphilitics at some time suffer from arthralgias. Wile and Senear[37] have studied 165 cases of early syphilis and have found that 60 of these cases showed either bone or joint involvement, in 21 instances the joints alone being involved, while in 12 both bones and joints were affected. Baets[38] reports that out of 100 cases of arthritis seen in the Canal Zone no fewer than 63 were of syphilitic nature. Other observers have reported that from 10 to 40 per cent of all syphilitics have some joint involvement.

Clark, writing in the *Journal of the American Medical Association* for Dec. 22, 1918, reports that in the Canal Zone 1100 consecutive autopsies have been performed and the joints examined in each instance. In 172 of these cases definite joint lesions were found, although less than 1 per cent of the total number of postmortems were done upon "arthritis suspects." In 96 instances the arthritis was due to syphilis. In this series the right knee was involved 90 times, the left knee 92 times, the right hip 17, the left hip 9, right shoulder 17, left shoulder 8, right elbow 2, left elbow 2, right ankle 2, left ankle 3, and the right wrist and spine once each. This would seem to prove conclusively that syphilitic arthritis is much more frequent than we have been led

to believe from the reports of the past, and that it is frequently present although it gives no clinical symptoms.

Time of Involvement.—Wile and Senear have definitely shown that during either the primary or secondary stage about 20 per cent of all cases show some symptoms referable to the joints. During the late stages of syphilis less than 5 per cent of all patients complain of arthralgia and an even smaller number have some more serious lesion.

Etiology.—There has been some discussion as to whether the Treponema pallidum or its toxins are responsible for the joint pains but as we learn more concerning the widespread lesions directly due to the organism, the opinion gains ground that the trouble is due to the local presence of the treponema. In the early cases trauma seems to play no great part in localizing the trouble, but in late cases trauma to a joint frequently precedes the development of the syphilitic affection.

Clinical Types.—After considerable observation and a careful reading of all available literature, we feel that in acquired syphilis the following clinical types can be recognized:

In early syphilis,
- Arthralgia.
- Synovitis—the pseudorheumatism of the French authors.
- Hydrarthrosis.

In late syphilis,
- Arthralgia.
- Synovitis.
- Hydrarthrosis.
- Osteochondroarthropathies,—the pseudowhite swellings of the French.
- Gummous perisynovitis.
- Charcot's joint of tabes.

In addition there are two other types which deserve brief mention, although we are not yet justified in classing them as clinical entities—namely the pseudoarthritis deformans of Mericamp and the hybrid forms of Weliaminoff.

Arthralgia.—The arthralgias are the simplest and most frequent joint lesions of syphilis. Gouriantz estimates that they affect about 8 per cent of all syphilitics, but many observers give a higher figure. They occur early in the course of the disease,

usually with the early rash, but sometimes with the chancre, and one of the authors has seen two cases where they preceded the development of the chancre. Any joint may be affected, but those most frequently involved are the large ones, namely the shoulders, knees, elbows, wrists and ankles. The pain may be either mono- or poly-articular and is usually worse at night. The symptoms are entirely subjective, there are absolutely no objective signs, and in several cases which we have had radiographed no joint abnormalities could be detected. Ordinarily the pain is increased on some particular movement, but sometimes is eased by movement. A previous injury seems to make a joint more susceptible. The course of the disease is essentially chronic if untreated, but antisyphilitic medication usually has a very prompt effect. It is important to note that while these lesions may occur during any stage of syphilis, they are not common during the late periods of the disease. Pathologically but little is known of them, but they are presumed to be due to the local development of reactions to the treponema in the joint tissues. The diagnosis can not be made from examination of the joints alone, but must be made from other signs of syphilis, either physical or laboratory.

Synovitis.—According to Pillon there are three types, the acute, the subacute and the chronic. The acute type may occur during any stage of syphilis, but is most frequent during the early florid manifestations. It may absolutely simulate acute rheumatic fever, for the symptoms are frequently intense, there being inflammatory swelling, pain and often high fever. The pain is severe and continuous and is aggravated upon movement. The lesions are usually localized in one or more of the large joints, but even the fingers may be affected. The swelling may be either articular or periarticular and may be very pronounced. The skin is red and may look phlegmonous. The temperature may reach 104°, but there is no definite type of fever. Antisyphilitic treatment usually causes prompt disappearance. In one such case which we recently had radiographed, no local lesions could be found except a trifling periostitis about an inch above the joint.

The subacute form is simply less severe than the form just de-

scribed; it may be subacute from the start, or an acute case may become subacute.

The chronic type is not so well known. This form is never associated with effusion, but is always of the "dry type." Fournier[39] thinks that the crepitating joints of old syphilitics may be due to an old mild chronic infection. However, treatment has no effect upon the group of cases that Fournier describes.

In all of these cases the diagnosis can not be made from phys-

Fig. 107.—In spite of the fact that the elbow joint was much swollen and very painful, the roentgen ray findings were negative. This was a typical case of pseudorheumatism. (Roentgenogram by Dr. Walter Van Sweringen.)

ical examination of the joints alone; both thorough physical and laboratory investigation are required. It can not be too strongly emphasized that every case of joint trouble, be it acute or chronic, should have a routine Wassermann done.

Hydrarthrosis or arthritis with effusion due to syphilis is probably not so rare as the few case reports in the literature would have us believe: it is considered unusual simply because it is not more frequently looked for. This form usually occurs

before the third year of infection, and Gerin-Roze has reported a case as early as the tenth day after the appearance of the chancre; it is most frequent with the eruption. The localization is variable: sometimes it is unilateral, but it may be polyarticular and is frequently symmetrical. The joints are affected in the following order of frequency: knees, elbows, wrists and ankles. The severity of the syphilitic infection appears to have no influence upon the development of these lesions. The onset is usually insidious, and the first symptoms are usually a little discomfort and swelling. Then the swelling appears and may develop very rapidly, although various writers disagree upon this point. The skin appears normal, there is no periarticular swelling and usually there is no pain, and but little limitation of movement; there is no muscle atrophy. While there is no evidence, either clinical or radiological, of epiphysitis or of hyperostitis pressure upon the head of the bone is almost constantly painful. Cytologic examination of the fluid fails to reveal the presence of the treponema. At the onset there are usually some polymorphonuclear leucocytes in the fluid, and later examination shows lymphocytes. The Wassermann is positive, as would naturally be expected. The course of the disease is chronic, and there is always a tendency towards recurrences. The condition is helped by rest and by antisyphilitic medication. The diagnosis from tuberculosis may be very difficult as Pillon points out, and can only be made by general physical and laboratory investigations.

It has been suggested that cases of true intermittent hydrarthrosis, a condition which is characterized by a periodic swelling of one or of several joints without fever, may be due to syphilis. However, in one case which the authors saw together there was absolutely nothing to substantiate this hypothesis. It should always be borne in mind that, as D'Arcy Power[40] points out, syphilis can give an intermittent effusion into the joints, the trouble, however, persisting for some considerable time.

Osteochondroarthropathies, the pseudowhite swellings of the French authors, are in reality due to destructive or proliferative gummous changes in the vicinity of joints, and occur only during the late stages of syphilis. This disease is not especially common, Fournier reporting but 30 instances among 5000 syphilitics. The knee is affected in about 60 per cent of the cases;

next in frequency rank the shoulders, elbows and wrists. Varying clinical pictures are presented according to the stage of the disease and the extent of the gummous changes. The lesions are most apt to begin in either the periosteum or at the edge of the epiphysis, and in the early stages different clinical findings would naturally result, as in the former case the swelling would be more localized at one side of the bone, whereas in the latter instance there would be a uniform bone swelling. During this early period there is usually nocturnal pain, tenderness on pressure, and no fever. As the swelling increases, the use of the joint is usually but little limited and the skin shows no changes. As the disease progresses, deformity may limit free movement, and if the synovial membranes become affected, effusion is prone to result. At this advanced stage the joint is globular, the overlying skin is thinned by distention, the muscles appear smaller, the limb is not held in an abnormal position; there is no ankylosis and no local adenopathy. The course of the disease may vary considerably: there may be spontaneous healing, and the resulting scar formation cause ankylosis or considerable deformity; fistulae may form and the development of sequestra prevent healing; the joint may become secondarily infected with the formation of pus.

This type of disease is extremely difficult to differentiate from tuberculosis, and unquestionably many syphilitics have been treated for tuberculous joints: at present the employment of the Wassermann reaction and of careful physical examinations for syphilis should almost invariably prevent such disastrous mistakes. The diagnosis can not be made from local examination alone, or from the history.

The roentgen ray findings will be fully discussed in the section dealing with the value of the x-ray in diagnosis.

Gummous perisynovitis is very rare and usually appears in from five to eight years after infection. The knee is most apt to be involved, but the elbow, wrist or ankle may be affected. The disease is usually monoarticular. The onset is insidious, there is first noticed a little swelling of the joint, often accompanied by but little pain. As the effusion increases the joint becomes globular, the overlying skin is white with distended veins. Some infiltration and often a distinct thickening of the

synovial membranes can be distinguished; frequently there is a peculiar "pasteboard" rigidity. There are no functional signs. No bone changes can be detected by the x-ray. If the disease remains untreated for a long time, there may result crepitation, due to destruction of cartilage, foreign bodies due to cartilage fragments, or even infection and ankylosis. This form is comparatively easy to diagnose, since there are no bone changes.

In general it may be said that the pathologic findings in gummous lesions of the joints are similar to such conditions in other

Fig. 108.—In late syphilis there may be complete destruction of the head of a bone so as to give a picture resembling Charcot's joint. Notice the periostitis of the radius. (Roentgenogram by Dr. Walter Van Sweringen.)

portions of the body. There may be one isolated gumma, or there may result a diffuse gummous infiltration with minute or miliary lesions, and a resulting fibrosis. The changes in the bones have been considered earlier in the chapter. The exact reaction of cartilage to the treponema is a problem that remains to be worked out.

The treatment of these lesions is similar to the treatment of syphilis in other portions of the body, namely, intensive arsphenamine and mercurial administration. Rest alone has no appreciable effect upon such syphilitic joints, although rest combined with antisyphilitic treatment is usually desirable.

Tabetic Arthropathy

Tabetic arthropathy, a joint affection coming on during or preceding the early stage of tabes dorsalis, was first described by Charcot[41] in 1868, and is generally known as Charcot's disease.

It is now conceded that tabes is a syphilitic affection, hence it would seem proper to include mention of Charcot's disease in a work upon syphilis. It must not be confused with syphilitic arthropathies, for it is generally believed that the pathologic processes taking place in the two conditions are not similar, the Charcot joint being a disintegration due to a loss of innervation, due to syphilitic disease of the central nervous system, and not to the direct action of the Treponema pallidum. In this respect it simulates the atrophic arthritis of Goldthwaite,[42] which is now thought to be a joint disintegration due to the action of the toxins of some general infection on the nerve supply to the joints.

A tabetic arthropathy usually affects but a single joint, but may affect symmetrical joints. The knees, ankles, hips and tarsal bones are more often affected than are the joints of the upper extremity. It occurs more often in men than in women, probably because there are more male than female syphilitics.

The time of onset seems to be of but little diagnostic value, for it may occur in either the prodromal or late stages of tabes. Kredel's[43] table is of interest in this respect; he reports 132 cases of tabes with arthropathies having the following time of onset:

Premonitory period	21
1st to 5th year	38
5th to 10th year	32
After 10th year	41

In one case, seen by one of the authors about fourteen years ago, the diagnosis of an oncoming tabes was made by x-ray examination, the diagnosis being based on the indistinctness of the

picture of the affected side in comparison with the clear picture of the other joint. This indistinctness was due to the fibrillary contractions. At the present time with more rapid exposures this would probably not hold true. Further observation of the patient verified the diagnosis.

One of us has recently seen another case in a young man with a badly swollen ankle, which had come on suddenly, where the disease was of but a few months' duration.

Lack of pain, even though the joint is far from functionating properly, is of great diagnostic value, but this is somewhat like true syphilitic arthropathy.

The pathologic process seems to start with a rapid exudation of fluid into the joint, and this rapidly extends to the surrounding tissues. With this there is a disintegration of the joint tissue, capsule, ligaments, cartilage and bone. As the swelling subsides, abnormal motion, free from pain, is a most pathognomonic sign.

Another interesting feature is the lack of muscular atrophy, or of but a limited amount of atrophy, although this is also a sign of true syphilitic arthropathies. This is doubtless due to the ability of the individual to get about without pain, the atrophy that accompanies other joint conditions is usually in direct ratio to the amount of pain on use. In other words atrophy is due to disuse.

The overlying skin is apt to be shiny, but not reddened, the first because of increased intraarticular pressure and the lack of the second to the absence of inflammation.

The x-ray findings are typical; there is a true disintegration and admixture of all the tissues, portions of bone for instance, being found at a considerable distance from their original locations. At times there appears to be a bone overgrowth, the so-called hypertrophic type; at other times there appears to be a special bone absorption, the atrophic type.

The pathologic findings are just what we should expect in a rapidly disintegrating joint; the synovial membrane is indurated with villous formation, the cartilage is thinned or frayed and there may be an ulceration or eburnation of bone.

The diagnosis should be based on the picture of a disintegrating joint, with little or no pain or discomfort other than that

due to the clumsiness of the joint. Other important signs are the Argyll Robertson pupil, the absence of knee reflexes, Romberg's sign, a rapid onset often associated with lightning pains, gastric crises. Tabes must be differentiated from syringomyelia and this can be done by noting the absence of the above signs and usually by the presence of trouble in varied joints. There is a marked alteration in sensation. Osler states: "The combination of loss of painful and thermic sensation with paralysis of an amyotrophic type is characteristic but not pathognomonic." In hypertrophic arthritis none of the above signs are present except bone overgrowth.

One of the authors (H. H. H.) feels that most cases of so-called Charcot's joint are in reality syphilitic joints. In the past year he has examined x-ray plates of ten cases, diagnosed as tabetic arthropathies, and in each instance there were positive findings of luetic lesions. The hypertrophic type is undoubtedly due to the direct action of the treponema. Other syphilographers have the same feeling. Stokes, of the Mayo Clinic, agrees with him in this. However, Baetjer, of Johns Hopkins, has stated that he has found a condition analogous to the Charcot's joint in syringomyelia. Evidently the whole question needs further investigation.

Pseudoarthritis Deformans (of Mericamp).—Fournier, Mericamp, Dumesnil, Danjon and Fouquet have described cases of arthritis deformans due to syphilis. More recently O'Reilly[44] has reported positive Wassermanns in some cases of arthritis deformans. According to the French authors it affects the large joints, especially the elbows and knees. The beginning is insidious. The most characteristic clinical finding is the deformity, for hyperostoses of the epiphyses and irregular bony outgrowths both limit movement and cause crepitation. Ordinarily treatment has no effect, but Schmidt has reported a case of hypertrophic arthritis that was cured by antisyphilitic medication. Pillon comments that these lesions resemble the deforming tuberculous rheumatism of Poncet.

Weliaminoff in 1910,[45] and more recently Gouriantz and Pillon have written of the hybrid forms of syphilitic arthritis, by which they mean either syphilis developing in a person who has tuberculosis, or a tuberculous joint or vice versa. The whole

question is so indefinite and unsettled that it is hardly worth discussing within the limits of a short text book article.

Other valuable references are those of Rubin,[46] Levine,[47] Higgins,[48] Bering,[49] Wiggs,[50] Hartlung,[51] Zears,[52] Wysocke,[53] Waterhouse,[54] Wallenberg,[55] Voss,[56] Voisine,[57] Frost,[58] Richet,[59] Patton,[60] Barrett,[61] Bronchin,[62] Crocq,[63] Ely,[64] Frauenthal,[65] Von Gies,[66] Virchow,[67] Rasch,[68] Morestin,[69] Rotter,[70] Krönig,[71] Power[72] and Hutchinson.[73]

Syphilis of the Muscles

According to Power[74] syphilis of the muscles was recognized as long ago as 1553 by Theodosius.[75] Four types are mentioned, first myalgia, second frank gummata, third diffuse myositis, and last a progressive weakening of the muscular power.

Myalgia is unquestionably comparable to arthralgia and is probably due to local reactions against invading organisms. There are no objective symptoms, but subjectively there is pain, usually worse at night and aggravated by movement. Points of tenderness can usually be determined. The muscles most frequently affected are those of the thighs and legs and the deltoids, but the shoulder muscles may also be involved. Treatment usually gives a prompt response.

Gummata are probably most frequent in the muscles of the tongue but may occur in any muscles, notably the triceps and abdominal. Usually a swelling is first noticed and this runs the usual course of gumma in any other portion of the body. Associated there may be diffuse syphilitic myositis. Thompson[76] states that calcification or ossification may occur. Sarcoma must be excluded, and rarely actinomycosis as in Koehler's[77] case. The prognosis is good.

Diffuse myositis is rare and is due to a diffuse infiltration of the muscles by miliary gummata, and is comparable to the same condition that so frequently affects the glands of the body. No redness and usually no tenderness is apparent, but the muscles become hard and contractures develop. In one case recently shown in Washington nearly all of the muscles of the body were affected, but as a general rule the process is limited to one or two, notably the biceps and gastrocnemius, flexors of the fore-

arm, pectoralis major, sternomastoid, masseter and abdominal muscles. When the disease is established but little is to be expected from treatment, although much comfort may be given.

Loss of power was first noticed by Fournier as occurring during the early stages of syphilis as measured by the dynamometer. During the secondary stage in untreated patients there may be intermittent trembling. Power believes that a neuritis is responsible.

Syphilis of the Tendons and Tendon Sheaths

Syphilis of the tendon sheaths, although rare, is more frequent than in the less vascular tendons. Inflammation of the former occurs in two forms, the serous and the gummous, while in the latter only gummata have been described.

Serous tenosynovitis usually occurs during the earlier stages of the disease and is a simple serous inflammation leading to effusion. It is most frequent in the tendon sheaths at the back of the wrist and in those on the front of the ankle, but may occur in the peronei or the hamstrings, as well as the biceps or supinator longus. According to Power the swelling begins rapidly and painlessly and does not interfere with movement. There is a soft crepitation felt accidentally on movement. The condition must be differentiated from tuberculosis but is usually more localized, neighboring structures not being affected. Treatment soon alleviates the trouble.

Gummous tenosynovitis occurs during the late stages in one of two forms, either diffuse or localized, and is rather more common than the type just described. Ulceration through the skin is the usual rule, but treatment usually results in speedy cure.

Gumma of the tendons merely leads to a thickening of the tendon and may result in calcification, although an ulcer may result.

Syphilis of the Bursæ

Syphilitic bursitis has been most fully described by Churchman,[79] who collected twenty-eight cases. It was first described by Verneuil[80] in 1868. The condition is rare, and but little has been written concerning it. Churchman's excellent description may be quoted:

"The picture, then, is one of an indolent affection of the bursæ, involving most often the knees—particularly in women. The disease is quite independent of syphilitic arthritis, the bursæ involved being most often those unconnected with the joints, and the neighboring joints themselves being entirely free from involvement. In the secondary stage simple hygroma is frequent; in the tertiary stage, gummatous, ulcerating, and fungous forms occur. The bursæ involved are those most exposed to trauma; but a study of the disease makes it clear that trauma, as usual in syphilis, only determines the site which the disease will occupy. There is little or no accompanying functional disability; and specific treatment leads to a prompt and permanent cure. In view of the marked indolence of the condition and its great similarity to the arthropathies of syphilis, it should be spoken of as luetic bursopathy (of Verneuil) the possibility of the rare occurrence of more acute symptoms being, however, kept in mind."

The conditions especially to be excluded are professional bursopathies, tuberculous and other chronic infections of the bursæ.

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CHAPTER XV

SYPHILIS OF THE GENITOURINARY ORGANS

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The initial lesion of syphilis, the chancre, occurs most frequently upon the external genitals. The disease is, therefore, most often venereal in its manner of approach or mode of infection. In this respect only, however, can it be considered a venereal disease. In its clinical course, its widespread distribution, involving, as it may, every organ and tissue of the body, syphilis is distinctly a constitutional disease.

The primary syphilitic sore has already been described in Chapter V. We shall consider here syphilis of the kidneys, ureters, bladder, prostate, seminal vesicles, spermatic cord, epididymes, and testicles.

It may be stated that in syphilis the urinary and genital organs, testicles excepted, enjoy a relative immunity from infection. And for that reason the subject has received scant attention in the current textbooks. But, as we shall see, this immunity is only relative. The number of clinical observations of syphilis of the genitourinary system recorded in the literature of the last decennium, in which the diagnosis was definitely established, exceeds the number previously reported. This suggests that these lesions are not rare and are not as uncommon as was formerly supposed.

SYPHILIS OF THE KIDNEY

According to Rose Bradford[1] syphilis may not only give rise to a nephritis, but this complication may occur at any period of the disease, and, further, various forms of nephritis are produced.

Acute syphilitic nephritis occurs as an early complication following infection. This form of nephritis, while presenting certain more or less characteristic clinical symptoms, is in general

comparable to the nephritis following any of the acute infective diseases. In its clinical, as well as pathologic aspects, it more closely resembles postscarlatinal nephritis. In addition to this form complicating the early or secondary stage of the disease, syphilis attacks the kidney in the late or tertiary stage, and gives rise to quite different pathological changes, more particularly interstitial changes, amyloid degeneration, and the formation of gummata. Furthermore, in congenital syphilis kidney lesions occur at two distinct periods; in early life associated with other visceral lesions and congenital stigmata, and as a late complication.

Syphilis has long been known as one of the causes of amyloid degeneration. And gumma has been considered as a rare but conclusive proof that syphilis may attack these organs. It is only comparatively recently, however, that the importance of syphilis as the etiologic factor in the production of nephritis, acute as well as chronic, has been recognized. Much greater attention has been paid to the subject by foreign authors. Comparatively few articles have appeared in American literature. The papers of Stengel and Austin,[2] and Stokes[3] are notable exceptions. Osler and Churchman[4] state that the subject has been widely overlooked and has received too little study.

It was thought for a long time that the urinary organs were peculiarly immune from infection with syphilis. Thus John Hunter in his treatise on the venereal disease (1786) wrote: "Many parts of the body, so far as we know, are not susceptible of the lues venerae. For we have not yet had every part of the body affected; we have not seen the brain affected, the heart, stomach, liver, kidneys, nor other viscera although such cases are described in authors." The weight of his great authority was felt for fully half a century. Rayer in 1840 was the first to point out the existence of syphilitic affections of the kidney and reported three observations. His views were not accepted, however, for a long time. A number of cases of chronic syphilitic nephritis and gumma of the kidney were reported during the following years, but attracted little attention.

The first paper on syphilitic albuminuria, the Thése of Guiol, appeared in 1867. In the same year appeared the important contribution of Perroud on acute syphilitic nephritis. To Perroud belongs the credit of first calling attention to the possi-

bility of an acute nephritis due to syphilis. The publication by Spiess of his observations upon 220 syphilitics coming to autopsy in which the kidneys were found intact in only 62 cases, and particularly that by Wagner of his study of 63 cases of kidney syphilis, had much to do with fixing attention upon syphilis as the cause of a variety of nephropathies. An important monograph was published by Mauriac in 1886. He emphasized the fact that now and then one sees cases of acute and subacute nephritis during the secondary stage which can be differentiated from the ordinary forms and which are cured by specific treatment.

In spite of numerous cases described by French, German, and English authors, as well as others, there have always been competent critics who have denied the specific nature of parenchymatous and interstitial nephritis following lues. In 1898 the whole subject of syphilis of the kidney was critically reviewed by Karvonen in an exhaustive monograph. Since this publication numerous papers have appeared chiefly in foreign journals as well as numerous monographs dealing with the various forms of syphilitic affections of the kidney. The discovery of the causative agent of the disease together with the development of the complement-fixation (Wassermann) test has given a new impetus to the study of syphilis. A renewed widespread interest in the subject has resulted. This is reflected in the number and character of observations upon syphilis of the kidneys recorded in recent literature.

Various classifications of syphilitic lesions of the kidney have been proposed. For the purpose of clinical study the following classification will suffice.

1. Secondary stage,
   Transient albuminuria.
   Acute and subacute nephritis—preroseolar nephritis.
2. Tertiary stage.
   Chronic interstitial and parenchymatous nephritis—
      Contracted kidney (Schrumpfniere).
   Amyloid kidney.
   Gumma of the kidney.
3. Congenital syphilis.
   Early nephropathies.
   Late lesions.

Secondary Stage

Transient Albuminuria.—During the period of incubation and especially associated with the appearance of the skin eruption a slight but definite albuminuria occurs. This has been reported by numerous observers. It has been noted much more frequently since an examination of the urine has become a routine procedure before the administration of arsphenamine. This is probably a toxic albuminuria associated with the general infection by the treponema and comparable to that associated with other acute general infections. Casts are never present, and other evidences of serious damage to the kidney structure are wanting. The albumin disappears rapidly under specific treatment. This must not be confused with the acute nephritis occurring during the secondary stage. The slight albuminuria, the absence of casts, red blood cells, and leucocytes as well as other symptoms of a true nephritis will serve to differentiate the two conditions.

Acute and Subacute Syphilitic Nephritis.—This form of nephritis, (nephritis acuta syphilitica precox of Hoffmann[5]) occurs at any time after the initial lesion. A form developing within a few weeks after the chancre and before the outbreak of cutaneous manifestations has been described. Thus Audry[6] records two cases, young men eighteen years of age, each presenting a typical chancre accompanied by adenitis. The duration of the chancres was three weeks and one month respectively. Examination of the urine disclosed quite unexpectedly a notable amount of albumin. This gradually diminished in amount and finally disappeared under repeated injections of arsphenamine. Audry believes these were cases of true syphilitic nephritis developing three and four weeks after the appearance of the chancre and before the skin eruption. Hoffmann has observed a similar case. Audry fails to understand why a general infection with treponemata should manifest itself first upon the skin. He believes that during the so-called period of incubation such localization may and does occur first in the viscera, particularly the kidneys. If this view is accepted, one can understand how in certain cases of nephritis, so-called precocious, the kidney lesion is in reality a long-standing one when its existence is first noted.

It seems reasonable to suppose that during the period of general invasion by the treponema the viscera are involved, but no symptoms may be produced by which such involvement can be recognized except in case of the kidneys. And the renal infection is recognized only because the kidney is more accessible than the other viscera. It may be recalled that not infrequently a macular eruption occurs on the bladder mucosa during the secondary stage which gives rise to no symptoms whatever and is easily overlooked without a routine cystoscopy. The same is true of other mucous membranes. Audry quotes Fournier as follows: "A diffuse acute and subacute nephritis can develop very early. Talmon has published a case of preroseolar acute nephritis in a young girl 21 years of age developing a few days after the appearance of the chancre. The quantity of albumin reached 32 grams per liter and disappeared rapidly without mercury. I have observed an acute nephritis developing in a man under exactly similar conditions before the appearance of the roseola. This subsided rapidly under a milk diet and mercury treatment."

This form of the disease may be easily overlooked, occurring as it does before the outbreak of the cutaneous rash. Its recognition is very important, however, in order that prompt treatment may be undertaken before serious damage to the kidneys has occurred. In this early stage the results of specific treatment are much more prompt and certain. And the prognosis is, therefore, more favorable than in cases developing at a later period.

Aside from the preroseolar nephritis which is characterized by its early onset and the absence of grave constitutional symptoms, acute syphilitic nephritis occurs in association with or subsequent to the outbreak of the cutaneous lesions. This complication may develop any time during the first two years, and especially during the first year after the primary sore. Dieulafoy[7] points out that the danger of nephritis is much less after the first year. The average period of onset is about the fifth month, although cases developing during the second and third months are common. The onset may be either abrupt or insidious, usually the latter.

The first symptom is usually edema of renal distribution. This develops rapidly and general anasarca may quickly result.

According to Dieulafoy acute syphilitic nephritis is distinguished by its sudden, early appearance, the severe grade of albuminuria, the enormous edema, and the frequency of pleural effusions and effusions into other serous cavities. The patient is little better than a sponge and dies saturated with serum. Rose Bradford insists, on the contrary, that dropsy is frequently absent. Hematuria is the first symptom in some cases and may be severe. In other cases, progressive weakness with anemia and loss of weight are the symptoms first noticed.

The urinary findings resemble those found in the more common forms of acute nephritis. The amount of urine is less than normal, it is clear amber or smoky, acid in reaction, with a high specific gravity. The sediment contains a few red cells, leucocytes, epithelial cells, and hyaline and granular casts. According to Munk, lipoid casts are numerous, but these are usually overlooked and classified as granular casts. The most distinctive finding is the large amount of albumin. The extraordinary grade of albuminuria which is characteristic of acute syphilitic nephritis is surpassed in no other form and is most closely approached in the postscarlatinal variety. Fifteen and twenty-five grams of albumin are not uncommon. In one case it reached the extraordinary amount of fifty-three grams (Decouts[8]).

Munk[9] has found doubly refractile lipoids in the urine of patients suffering with severe forms of nephritis. He believes there is a peculiar relation between syphilitic nephritis and the presence of these lipoids in the urine. A microscope provided with a Nicol prism is necessary for their demonstration. Under an ordinary microscope these lipoids appear as fat globules, but under polarized light they show a dark central cross separating four bright peripheral quadrants. According to Stengel and Austin lipoid globules have been found normally in certain tissues, for example, in the adrenal cortex, thymus, lutein cells, the puerperal uterus, mesentery, and choroid plexus. Pathologically they have been found in atheroma, amyloid kidneys, chronic nephritis with marked cellular degeneration, in the urine of nephritis, in albuminuric retinitis, in the epithelium of the pulmonary alveoli in pneumonias and tuberculosis, in neighboring lymphatics and the sputum, in the gall bladder and hepatic ducts during cholangeitis, in pyogenic membranes,

chronic mastitis, mesenteric tabes, actinomycosis, xanthomata, and in certain neoplasms (carcinoma, sarcoma and lymphosarcoma).

These authors report a series of twenty-three cases showing an abundance of albumin and casts in which six cases with a positive Wassermann all showed lipoids in the urine. In fourteen nonsyphilitics only five showed the presence of lipoids. And they add that with but one exception the cases which showed an abundance of the lipoids were syphilitic. It would seem, therefore, that while the presence of these globules in the urine in the case of a severe nephritis can not be considered specific, an abundance of lipoids present in such cases is highly suggestive of syphilis.

Up to the present time the discovery of treponemata in the kidney tissue has not been reported. If future investigations should demonstrate these organisms in the renal tissue, the direct evidence of syphilitic infection of the kidneys would be supplied.

Hoffmann reports the finding of the living Treponema pallidum in the urinary sediment in one of his cases, and refers to a similar observation by Dryer and Toepel. A similar report by Vorpahl[10] is not convincing. These are important observations, but so far they lack confirmation by other investigators. Great care must be taken to avoid contamination by lesions of the urethra, hence the urine for examination must be obtained by catheterization. The accuracy of these observations should be confirmed or disproved and if confirmed another valuable laboratory aid to the differential diagnosis of syphilitic nephritis will have been established.

Pathology.—The kidneys in acute syphilitic nephritis are enlarged, the cortex is thickened, and the capsule strips easily. They belong to the group of large white kidneys. The histologic changes resemble those seen in scarlet fever. There is a diffuse epithelial or parenchymatous inflammation. The epithelium of the convoluted tubules is chiefly affected. There are no glomerular changes and the interstitial tissue is not involved.

Diagnosis.—As pointed out by Stengel and Austin there is no morphologic picture by which the antecedent infection in any given case of nephritis can be identified. The recognition of the

etiologic relationship is based upon the sequence of kidney disease following a well-defined infection. In the absence of any histologic evidence the proof of the syphilitic nature of the nephritis is indirect. The diagnosis is therefore based upon the following criteria: (1) The proof of recent syphilitic infection. (2) The association of nephritic symptoms with the symptoms of recent syphilis. (3) The absence of other causes of nephritis. (4) The special features of the disease. (5) The urinary findings. (6) The therapeutic test.

There should be little difficulty in establishing the proof of recent syphilis. In doubtful cases the Wassermann test is of the greatest value. A negative history does not exclude syphilis since the initial lesion may be inconspicuous, attract little attention, or it may be overlooked altogether especially in women. The association of nephritis with well-marked symptoms of syphilis furnishes strong presumptive evidence of the specific nature of the nephritis, particularly in the absence of other manifest causes. If the nephritis presents the special clinical features recognized as characteristic of syphilis and these clear up under appropriate antisyphilitic treatment we must consider the proof conclusive.

That the symptoms of syphilis may be obscure and easily overlooked is too well known to require emphasis. Hoffmann points out that the edema of acute syphilitic nephritis may completely mask the eruption on the skin and mucous membranes. The literature records a number of cases where a nephritis persisting in spite of appropriate treatment led to a more careful examination and the disclosure of inconspicuous signs of syphilis. Under specific treatment the nephritis promptly subsided. The absence of an adequate cause for nephritis in any given case should arouse suspicions of syphilis (Fournier).[11]

The clinical features of syphilitic nephritis have already been referred to—insidious onset without definite cause, rapid development, the severe grade of albuminuria, and marked edema. The most constant characteristic is the abundant albuminuria. The presence of abundant lipoids in the urine in any suspected case is highly suggestive of syphilis. The urinary sediment should be examined for living treponemata. The therapeutic

test is undoubtedly the most reliable single aid in the diagnosis of syphilitic nephritis.

In certain cases there may be some difficulty in differentiating between syphilitic nephritis and a nephritis due to mercury. Confusion is most likely to occur in patients on mercury treatment having a marked albuminuria when they first come under observation. The importance of differentiating between a nephritis due to treatment and that due to the disease is obvious. In such cases treatment by mercury should be suspended at once and a careful note made on the behavior of the albuminuria. If due to mercury this will gradually subside. If the albumin does not entirely disappear after suspension of mercury treatment one can not exclude syphilis as a causative factor in its production. One should then have recourse to arsphenamine given cautiously in fractional doses. As pointed out by Stokes the substitution of arsphenamine for mercury is an easily available means of establishing the syphilitic character of an albuminuria, when previous mercurialization has confused the picture.

In any case of nephritis developing under treatment with mercury, confusion is less likely to occur. Frequent examination of the urine will detect an albuminuria before it has reached a grade where the two forms are apt to be confused. The onset of a mercurial nephritis is characterized by diuresis and cylindruria, features which readily differentiate this form from a true syphilitic nephritis.

It must be remembered, however, that true syphilitic nephritis may develop while the patient is under mercurial treatment. In other words, active mercurial treatment does not always prevent the development of a true syphilitic nephritis. The characteristic features of these two forms of nephritis already referred to should prevent confusion in properly conducted cases. Arsphenamine administered with care and judgment, is indispensable in the treatment of these patients.

Treatment.—The same general principles governing the management of other forms of acute nephritis apply to the treatment of acute syphilitic nephritis. The diet should be bland and unirritating to the kidneys. A rigid milk diet is recommended by some. Others insist that a more liberal diet, especially meats.

is necessary to keep up the strength and general nutrition of the patient. The general aim should be to restrict the proteins and salt, at the same time maintaining the body weight as far as possible by a liberal bland diet.

Most writers have emphasized the value of mercury in the treatment of this form of nephritis at the same time pointing out the danger from its use. Improvement under this drug is often prompt and striking. The results are much better when the condition is recognized early and treatment promptly instituted. Karvonen[12] goes so far as to question the diagnosis in any case not improved by mercury. On the other hand an increase in the albumin and casts has been noted following its use (Billings,[13] Munk). But Munk has suggested that this may be due to the diuresis and the flushing out of the kidneys. Marlot states that the improvement is often slight and transient and in one-third of the early cases and in an even larger number of late cases the issue is fatal in spite of all treatment. Mercury should be given by inunctions or intramuscular injection. The dosage should be carefully guarded at first to avoid kidney irritation and the production of mercurial nephritis. Hoffmann recommends a dose of two grams by inunction, half the usual dose. It is probably safer to begin treatment by the intramuscular injection of a soluble preparation, the biniodide or succinimide, and follow this by inunctions. Bauer[14] emphasizes the necessity for intensive treatment, especially in the less acute forms since in his experience the Wassermann will remain positive unless treatment is pushed vigorously.

As pointed out by Marlot and emphasized by Stokes, it is difficult to evaluate the usefulness of arsphenamine in the treatment of acute syphilitic nephritis on account of the small number of recorded cases. When this remedy was first introduced, renal complications according to Ehrlich constituted a definite contraindication to its use. And the cases of hemorrhagic nephritis following its administration reported by Nanta and others served to further discourage its use. However, it was inevitable that in these desperate cases, both acute and chronic, arsphenamine would be employed; and experience has shown that in such cases it is no more irritating to the kidneys than mercury; and the therapeutic results appear to be better. In a review of the litera-

ture Marlot found only eleven cases: six with late involvement and five of the precocious type. Of the six late cases there was only one cure (Lesser). Four were improved and one died. The latter was a desperate case and death was inevitable and should not be attributed to the arsphenamine (Gourget).[15] Of the five early cases there were three cures, one failure, and one death. Here again the fatal case can not be charged to the arsphenamine according to the same critic. These results are encouraging when one remembers that these patients were previously treated by mercury without success. It is further pointed out by Marlot that in the four cases showing improvement this followed one injection. When no improvement occurred or the condition was aggravated after the first injection, subsequent injections were useless. In other words if arsphenamine is to be of any benefit the first injection will show it. In one case (Widal) improvement was not noted before the eighth day and continued for a month. Hence it is suggested that injections should not be repeated under fifteen days. It is further evident that the more chronic cases are less favorably influenced by arsphenamine.

Gourget concludes from his review that there can be no doubt that arsphenamine is effective against syphilitic nephritis, but it can not be considered inoffensive. Munk reports favorably on its use, likewise Hoffmann, Audry, Stokes, and others. Although reports are somewhat confusing, arsphenamine in proper dosage rarely if ever causes albuminuria.

To summarize: no hard and fast conclusions can be drawn from the relatively few cases reported. The evidence at hand, however, indicates that arsphenamine is most valuable in the treatment of syphilis of the kidney. It is less irritating than mercury and is, therefore, preferred in acute cases where irritation of the kidneys should be carefully avoided. Arsphenamine is more efficient than mercury in combating the specific agent of the disease. It should be given in small doses, 0.15 to 0.2 grams intravenously. If no improvement follows the first injection, no benefit may be expected from subsequent injections. In the presence of degenerative changes in the kidney and in cases of renal impermeability, little or no benefit can be expected from any antisyphilitic treatment.

Tertiary Stage

Chronic Parenchymatous and Interstitial Nephritis.—In certain cases of chronic parenchymatous and interstitial nephritis the etiologic factor must be sought in an antecedent syphilis. It is a curious and interesting fact that while it is easier to definitely establish the etiologic relationship of syphilis in the acute forms of nephritis, syphilis of the kidney was first recognized in the form of chronic nephropathies, chronic parenchymatous and interstitial nephritis, amyloid degeneration, and gumma. Thus Rayer who first recognized clinically the existence of syphilitic affections of the kidney records three cases in his *Traité des maladies des reins* published in 1840: two of chronic interstitial sclerotic nephritis and one of amyloid degeneration. Beer in 1858 described a case of gumma of the kidney and in a later publication (1867) described four different forms of kidney syphilis. Lancereaux in his *Traité de la syphilis* published one year earlier (1866) recognized three forms of the disease, interstitial nephritis, gumma, and sclerotic kidney the end result of the preceding forms. Spiess found in his series three cases of chronic parenchymatous and interstitial nephritis, thirteen of partial interstitial nephritis, and eighteen cases of kidney atrophy. Wagner records seven cases of granular kidney and six of unilateral atrophy among sixty-three cases studied.

More recent authors have not only accepted syphilis as the causative factor in many cases of chronic nephritis, but insist upon the importance of differentiating this group of cases. Thus Munk states that in addition to the acute nephritis, syphilis produces a chronic indurative nephritis, nephritis interstitialis chronica fibrosa multiplex (Orth). This must be distinguished from the ordinary arteriosclerotic variety (schrumpfniere) just as we distinguish syphilitic aortitis from the other forms in order that appropriate treatment may be applied. This process affects only scattered areas of the kidney.

Symptomatology.—By means of the Wassermann test Munk has attempted to differentiate these two forms and from a study of the specific group to build up a more or less definite clinical picture of chronic syphilitic nephritis. He points out the following characteristics: The disease develops at a late period after

infection. Polyuria is not as marked as in the ordinary form. Urinary sediment is small in amount. Albuminuria is abundant and with a lipoiduria may persist for years without any associated vascular changes. Marked anemia is quite characteristic and may be associated with enlargement of the liver and pancreas. The disease occurs at a time when arteriosclerosis does not appear, from twenty-eight to thirty-seven years.

According to Neumann the hyaline casts are narrower and smaller than in the ordinary forms of chronic nephritis. He concludes that the characters of chronic syphilitic nephritis are not as well defined as in the more common form of the disease, hence diagnosis is more difficult and is more often made at autopsy. The most important features of the clinical history according to Bauer are the abundant albuminuria with low specific gravity, the absence of vascular changes and low blood pressure, and an absence of anemia in spite of a long-continued albuminuria, often over a period of years. Particularly important is a markedly positive Wassermann reaction. This Bauer considers pathognomonic.

Diagnosis.—When the kidney lesion is associated with amyloid degeneration and symptoms of tertiary syphilis of other organs, liver, spleen, pancreas, aorta, etc., the diagnosis may be fairly easily made. In the less chronic cases when the infection has occurred years before, the diagnosis is extremely difficult. All other causes of the disease must be carefully excluded. A very strongly positive Wassermann is suggestive (Bauer). An abundant albuminuria persisting for a long period with lipoiduria but without associated vascular changes should arouse suspicions of syphilis. Munk calls attention to the x-ray findings which show the heart and aorta of the same type as in syphilitic aortitis, while in ordinary chronic nephritis the heart and aorta show the type seen in arteriosclerosis. The therapeutic test should be applied in case of doubt, but this is not as helpful as in acute syphilitic nephritis, since the response to specific treatment is not likely to be so prompt or so striking, and will often fail completely.

Faroy[16] reports the finding of treponemata in the lumen of the tubules, but none in the tissues in a patient dead of amyloid disease. This observation is of interest chiefly in its bearing on the

question whether the kidney changes are due to the organisms or to their toxins. Bauer believes the lesions are the result of a toxemia.

Treatment.—In long-standing cases with amyloid changes little or nothing can be expected from specific treatment. As Dieulafoy puts it, "waxy degeneration in old syphilitics is a tenacious and irremediable lesion." Likewise unfavorable are the cases with secondary changes in the parenchyma. In less chronic cases in which extensive degenerative changes have not yet occurred improvement may be obtained by antisyphilitic treatment. Arsphenamine is better adapted than mercury as it is less injurious to the kidney and more effective against the disease (Bauer). According to this same author infection in these cases is intensive and demands vigorous treatment. Arsphenamine is well borne according to Munk who recommends a dosage of 0.2 to 0.3 grams. Mercury should follow the administration of arsphenamine. This is well borne if care is used in beginning with intramuscular injections of small doses of a soluble salt and this is followed by inunctions.

Amyloid Kidney.—Syphilis has long been recognized as an etiologic factor in the production of amyloid or waxy degeneration of the kidney. This degenerative change results apparently from the long-continued action of toxins. Syphilis differs from all other infectious diseases in that in addition to presenting the symptoms and sequelæ of an acute infection, the disease may persist for a great many years in an apparently latent form and finally give rise to degenerative changes in the various organs and tissues of the body. Thus amyloid degeneration must be looked upon as the result of a long-continued toxemia associated with chronic forms of the infection. It is a degenerative process occurring in the tertiary stages of the disease as well as in the congenital variety.

These patients usually present other tertiary lesions, for example, the skin and viscera. They are anemic, digestion is bad, and the general condition is poor. Occasionally there is edema of the face or lower extremities. The urine contains an abundance of albumin, but there is rarely any increase in arterial tension. There is often an enlargement of the liver and spleen.

Amyloid of the kidney is peculiarly resistant to all treatment, and death usually occurs with increasing cachexia.

Gumma.—Gummata of the kidney are habitually multiple, and vary in size from a hazelnut to a walnut. More rarely the whole organ is involved in a single large gummous tumor. Gummous deposits are usually present in other organs, liver, spleen, testicle, etc. When the gummata are limited to the cortex the remainder of the kidney may appear quite normal, more often it is lobulated and scarred or enlarged and amyloid.

Seiler studied the symptoms in one case over a period of years. The diagnosis in this case was confirmed by autopsy. There was an intermittent albuminuria with blood and detritus in the urine. Subjective symptoms were absent. In large gummous tumors there may be local pain, tenderness, and discomfort due to pressure.

Chevassu[17] groups the cases of gumma of the kidney into three categories:

1. Autopsy cases. A considerable number have been reported.
2. Nephrectomy cases. Israel (two cases), Bowlby,[18] Chevassu (one case each).
3. Clinical observations. Margoulies, Hirsch,[19] Moritz.

Bowlby's patient was a woman, aged 40 years, with an exceedingly hard, easily movable, renal tumor. Infection occurred twenty-three years before and for eighteen years there was no evidence of syphilitic disease. The urine was normal in quantity, with a slight trace of albumin, but contained no casts or blood. At operation a hard, nodular tumor weighing 17 ounces was easily shelled out. Almost all trace of kidney tissue had disappeared, and except for the shape of the mass it bore little resemblance to a kidney. Microscopic examination showed typical gummous areas with small-celled infiltration and caseous degeneration. This patient was rapidly cured.

Syphilis of the Kidney Pelvis

Syphilitic infection of the pelvis of the kidney is rarely observed. Only a few cases are recorded in the literature. Gottfried[20] reports one case of unusual etiology. A young man wishing to escape military service injected a yellow fluid (urine?) into his bladder. This was followed by a cystitis, bilateral pye-

litis, and a left pyelonephritis. No organisms were found in the catheterized kidney specimens. The condition persisted in spite of bladder and pelvic lavage with silver nitrate. A positive Wassermann test was then found. There were no other evidences of syphilis and no organisms were found in the urine. After five injections of mercury salicylate the urine cleared up. Eight months later the Wassermann test was negative, the urine remained clear and was free from albumin. According to Gottfried similar cases are reported by Hadden, Aufrecht, and two recent ones by Welz.[21]

Paroxysmal Hemoglobinuria

The association of syphilis, particularly congenital syphilis, with paroxysmal hemoglobinuria has long been noted. This relation is interesting since hemoglobinuria occurs in other protozoan diseases, for example, in piroplasma disease of horses and in malaria (Barker). Just how frequently syphilis is associated with this disease is still undetermined. Stempel found a history of syphilis in only 29 per cent of 77 cases. Macalester found evidence of syphilis in 60 per cent of 39 cases collected from the records of Guys Hospital. Dieulafoy states categorically that lues is present in 50 per cent of these cases. It must be borne in mind that until recently the only conclusive evidence of syphilis was the presence or previous occurrence of syphilitic symptoms, and this evidence was wanting in many cases. Thus, Garrod states the matter as follows: "In some cases this malady would appear to have a syphilitic origin * * * but not infrequently no such antecedent cause could be traced."

From a study of the Wassermann reaction in hemoglobinuric patients Browning and Watson conclude that a positive reaction in the majority of cases, together with other collateral evidence, constitutes a very strong basis for the opinion that syphilitic infection is practically invariably present in cases of paroxysmal hemoglobinuria *e frigore*. They state further that the occurrence of a positive Wassermann test is a feature almost as constant as in cases of general paralysis. There are 59 cases of paroxysmal hemoglobinuria recorded in the literature in which a Wassermann test was made. It was positive in 53 cases, or 90 per cent.

Recent hematologic studies have shown that the plasma of hemoglobinuric patients contains a complex hemolysin of amboceptor-complement nature. At a low temperature the amboceptor combines with the red corpuscle. Subsequent elevation of the temperature causes union of the complement, and hemolysis occurs.

Hoover and Stone state as the result of their study that the lytic substance present in the blood of these patients is a biologic product of some form of infection. But as pointed out by Moss all efforts to find an infectious agent in the blood have failed. And he adds that of all suggestions so far made that of congenital syphilis seems to have the most evidence in its favor. In the two cases recorded by Moss the Wassermann test was positive.

SYPHILIS OF THE BLADDER

Historical.—Syphilitic disease of the bladder has been considered a rare affection. In the older text books it is not mentioned at all, dismissed very briefly, or its existence even is denied. In the most recent works the disease is considered so rare as to merit only the briefest mention. Within the past sixteen years, however, a considerable number of carefully studied cases have been recorded in widely scattered reports. These furnish sufficient data for a fairly comprehensive clinical study.

The history of this affection falls naturally into three periods. The first comprises those rare observations upon syphilitics coming to autopsy in which ulcers, tumors, or perforations of the bladder were discovered and were considered syphilitic in origin. This period extends to 1879 when Proksch critically reviewed all the published cases up to that time. He found only six cases which could be considered definitely proved (Morgagni, Ricord, two cases, Virchow, Vidal di Cassis, Tarnowsky).

To the second period belongs a small number of cases observed clinically in which the diagnosis was confirmed by the disappearance of all symptoms following antisyphilitic treatment. (Morris, Griwzow, two cases, Chezelitzer, Margoulies, and Towbien.) No direct examination of the bladder lesion was made.

The third period begins in 1900 when Matzenauer published

his case and described for the first time the cystoscopic appearance of tertiary syphilis of the bladder. During the past sixteen years the number of observations has rapidly increased so that up to the present time about forty cases have been reported. In 1909 it was discovered that the bladder is involved in the secondary stage. According to Levy Bing a systematic examination of the bladder during the secondary stage of the disease will show that a more or less characteristic erythema resembling the roseola rash on the skin and superficial ulcerations are not rare. As these produce few or no symptoms they may be easily overlooked without a routine cystoscopic examination.

Etiology.—Lesions of the bladder occur during the secondary and tertiary periods of the disease. In the parasyphilitic diseases the bladder is commonly involved, notably in tabes. Age and sex have no influence upon the development of the bladder lesions. As tabes occurs more frequently in males, however, the associated bladder disturbance is more often observed in this sex. More common in middle life, cases occurring at the two extremes have been observed: at four years (Tarnowsky), and at sixty-six years (Gayet and Favre).

The secondary lesions usually appear within a few months after infection and are generally accompanied by lesions of the skin and other organs. Tertiary lesions, on the contrary, appear after a much longer period, up to twenty-five years. The bladder lesion may be the only evidence of the disease. In other cases the active syphilitic lesions of other organs or healed scars may be found. The majority of cases so far recorded belong to the tertiary period. It is quite probable that involvement of the bladder during the secondary stage would be observed more frequently if a routine cystoscopic examination were made. The occurrence of mild symptoms of cystitis during this stage are easily overlooked. These are attributed to the usual causes and their relation to a specific infection is not considered, particularly as they disappear under arsphenamine and mercury.

Secondary Syphilis

Nine cases of secondary syphilis of the bladder have been reported, six males and three females. The youngest was a

child four years old infected by its nurse. At autopsy extensive ulcerations of the mucous membranes including bladder and urethra were found. The liver was syphilitic. In all cases the bladder lesions were accompanied by secondary syphilis elsewhere, skin, mucous membranes, etc. Macules, papules, and ulcerations have been described. Duroeux has described a macular eruption resembling the roseola of the skin. In Fenwick's case (postmortem) papules were disseminated over the bladder mucosa resembling condylomata. The ulcers are usually multiple, two to twelve, rounded or oval, superficial, with a slightly elevated edge and a necrotic base. They occur most frequently about the ureteral orifices, but may be found in other parts of the bladder. The adjacent mucosa is edematous, hyperemic and the vessels are injected and prominent. The remainder of the bladder appears normal.

The symptoms of the secondary stage vary with the location and character of the lesion. In the case of Levy Bing there were absolutely no symptoms referable to the bladder, and the vesical lesions were discovered during routine cystoscopy.

With ulcerations at or near the vesical neck, symptoms of cystitis more or less acute are observed. Frequency, urgency and tenesmus may be marked day and night and not influenced by rest. Pain is then a constant symptom referred to the suprapubic area or perineum and radiating along the urethra, to the rectum and to the lumbar region. Hematuria when present is never profuse and is always terminal. The bladder capacity is reduced and varies with the intensity of the symptoms.

The urine is often perfectly clear. In the presence of infection it is turbid due to the presence of pus and organisms. It may be bloody from the presence of red blood cells. The presence in the urine of the treponema has been reported, but this observation has not been confirmed.

Tertiary Syphilis

By far the greater number of cases of bladder syphilis so far observed belong to the tertiary stage of the disease. This may be due to the more pronounced symptoms associated with tertiary vesical lesions. Attention is thus directed to the bladder

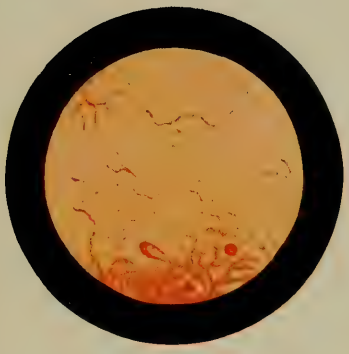

Fig. 109.

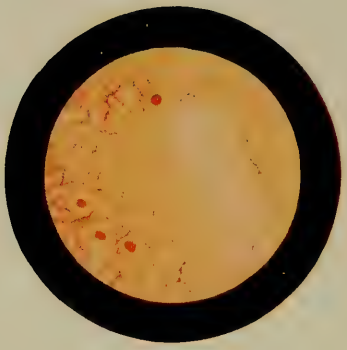

Fig. 110.

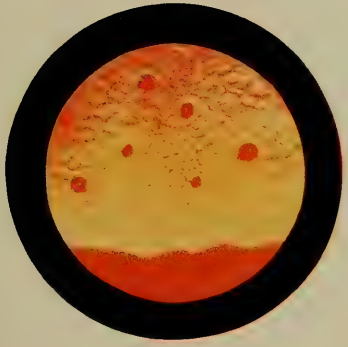

Fig. 111.

Fig. 112.

Secondary Syphilitic Lesions of the Bladder

Fig. 109.—Male, twenty-eight years, presenting secondary lesions of syphilis. Two small superficial ulcers at the base of the bladder which was otherwise normal throughout. Complete healing after four injections of salicylate of mercury. No local treatment.

Fig. 110.—Male, twenty-seven years, with lesions of secondary syphilis. Four superficial ulcers at vertex of the bladder. No other vesical lesions. Healing after seven injections of salicylate of mercury.

Fig. 111.—Male, age not stated, with cutaneous lesions of secondary syphilis. Cystoscopic: injection of vessels, marked edema of the vesical sphincter, numerous superficial ulcers scattered over the bladder wall. Symptoms: frequent and painful urination. Healing after ten injections of mercury. No local or internal treatment.

Fig. 112.—Same as Fig. 111 after treatment. (From Pereschiwkin: Ztschr. f. Urologie, 1911, p. 732.)

and examination reveals the true specific nature of the trouble.

Gummata of the bladder develop insidiously like all new growths and in the early stages produce little or no disturbance. Urination is slightly more frequent and associated with mild discomfort in the region of the bladder, in the perineum, or urethra. Hemorrhage, sudden in onset and profuse, may be the first and only symptom noted. More often symptoms of cystitis develop and increase rapidly in intensity.

Hematuria is the most constant and most striking symptom of tertiary bladder syphilis. It closely resembles the hemorrhage of new growth of the bladder. It appears suddenly without pain and is uninfluenced by rest or posture. It may continue for days, or weeks, and gradually subside only to recur after a longer or shorter period. Complete retention may result from the formation of clots within the bladder. As a rule, hematuria increases in severity with the duration and progress of the disease. Very exceptionally it may be absent altogether (Picker's case).

Pain is an inconstant symptom and varies with the location of the lesion and the presence or absence of infection as a complication. In Simon's case the patient complained of a dull dragging pain in the hypogastrium which had existed for two years. At first intermittent, it became constant day and night and increased as the bladder filled. In some cases pain is a marked feature of the clinical picture. It is likely to be more severe at the end of urination when the ulceration is located at the bladder outlet and is accompanied by violent tenesmus. Frequency of urination is a disturbing symptom in most cases. Slight at first it rapidly increases until the patient voids every few minutes with pain and tenesmus. While the symptoms in advanced, long-standing cases are very severe and distressing, the absence of marked symptoms in the presence of severe bladder lesions in the earlier stages is noteworthy. The development of the more acute symptoms probably coincides with the degenerative changes in the gummata and ulcer formation. Very often the bladder lesion is the only evidence of syphilis to be discovered. In the absence of a definite history the specific nature of the disease is not suspected.

Cystoscopic Appearances.—As viewed by the cystoscope two

varieties of lesions occur, gummous ulcerations and papillomatous growths. The former are more common, the latter are rare. They occur separately but may exist together.

Such ulcers are formed by the breaking down of a gumma of the bladder wall at its center. They are usually multiple, one to three, rounded or oval and vary in size, the largest being 1.5 cm. to 2 cm. in diameter. They are elevated above the bladder wall, projecting into the bladder cavity. They present a punched-out appearance with irregular borders, and a grayish necrotic base. Upon the base of the ulcer one sometimes observes the necrotic material detached in places leaving a red nodular surface which bleeds freely. The surrounding mucous membrane is edematous, hyperemic, and dark red or livid in color. The vessels are markedly injected and prominent.

The papillomatous lesions are very rare. In Margoulies' case (Case 1) there were three small growths the size of a small bean situated close together and located upon the base of the bladder just outside the ureteral orifice. The appearance of these growths suggested cancer of the bladder and an operation was advised. It was by mere accident that the operation was not performed, and iodide of potash was administered. Prompt disappearance of the lesions followed.

Gayet and Favre report a case (Obs. 2) of sclerogumma of the bladder and prostatic urethra. The bas-fond was elevated, thickened and reddened, and indurated. The fiery red surface presented a few small ulcers and numerous fissures giving the appearance of cerebral convolutions. The general appearance resembled that seen in cancer of the cervix which had involved the bladder wall. The same character of lesion is described by Picot.

Syphilitic lesions of the bladder both secondary and tertiary develop slowly and show no tendency to heal spontaneously. The long duration of symptoms in the reported cases is a striking feature of the clinical history. The secondary lesions are superficial; the tertiary involve the deeper layers of the bladder wall and unless arrested may result in perforation. Such a perforation developing rapidly and involving the peritoneal surface may terminate in fatal peritonitis. If the process develops more slowly a loop of bowel may become adherent to the bladder and

Tertiary Syphilis of the Bladder

Fig. 113.—Syphilitic ulceration of the bladder. Male, age sixty-six years. Chancre at twenty-two years. Hematuria and painful urination for six months. Lesions disappeared after ten injections of calomel and one of neosalvarsan.

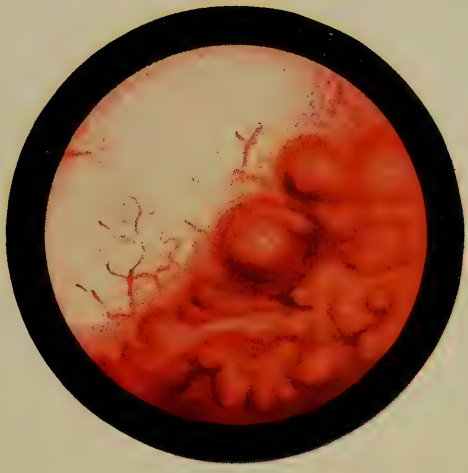

Fig. 114.—Gumma at the vesical neck. Female, age fifty years. Profuse hematuria for eight days and painful urination. This form of bladder syphilis is easily mistaken for new growth. Several such cases have been described.

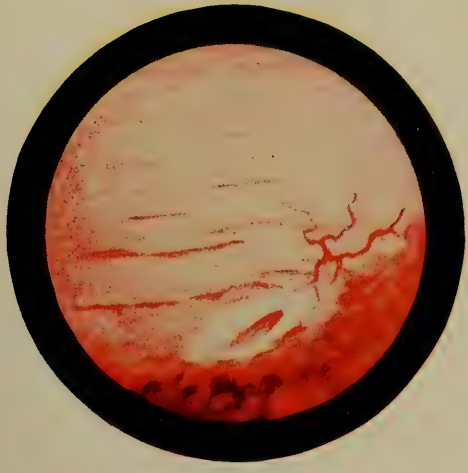

Fig. 115.—Appearance of the lesion after one month's treatment with three injections of neosalvarsan. Cystoscopy ten days later showed a normal bladder.

(From Gayet and Favre: Journal d' Urologie, vi, 45.)

perforation into the bowel occurs. Thus syphilis is one of the etiologic factors in the production of vesicointestinal fistula. Vesicorectal or vesicovaginal fistula may result from the perforation of the bladder base.

Treatment.—A striking feature of bladder syphilis is its prompt response to specific treatment. This is characterized by the immediate subsidence of all symptoms and the gradual disappearance of the vesical lesions. On the other hand the measures usually employed in the treatment of ordinary cystitis have no influence whatever on the symptoms or lesions.

Profuse and persistent hematuria which is often the presenting and predominant symptom quickly subsides and disappears completely in a few days after beginning mercury or the administration of arsphenamine. No less striking is the prompt subsidence of all signs of vesical irritation—frequency, urgency, tenesmus—and a gradual return of the vesical capacity to normal.

The gradual healing of syphilitic lesions of the bladder may be observed by repeated cystoscopy. At the second congress of German urologists, Ernst Frank presented a series of cystoscopic photographs demonstrating the gradual healing and final disappearance of these lesions under treatment. Similar demonstrations have been made since by other observers.

It is the strikingly rapid subsidence of symptoms under specific treatment that makes the therapeutic test so valuable in differentiating syphilitic from nonsyphilitic vesical lesions.

The Bladder in Parasyphilitic Diseases

It has been known for a long time that in the course of certain diseases of the nervous system (tabes, general paralysis), which we now designate as parasyphilitic, the bladder is involved indirectly. In tabes the disturbance of the bladder function may be the first and for a long time the only evidence of a cord lesion. This disturbance in bladder function is due to an interference with the innervation of the bladder musculature and its sphincters. The act of urination demands a finely adjusted and delicate coordination between the detrusor mechanism of the bladder and its sphincters. Stimulation and contraction of the detrusor muscles is coordinated with the inhibition and relaxation of the

sphincter mechanism. Interference with this delicate adjustment results in the inability of the bladder to properly empty itself. The degree and character of disturbance of bladder function in tabetics will depend, therefore, upon the character and extent of interference with the nerve supply.

The symptoms in many cases are strikingly similar to those observed in prostatic obstruction: difficulty in starting the stream, voiding in a small stream without force, frequency, intermittent flow—pumping urine out in successive efforts—marked straining on urination, incontinence of urine especially at night (bed wetting), and retention of urine, partial or complete. In one early case the patient consulted me because he had passed no urine for twenty-four hours. He had no discomfort whatever, but was alarmed because, as he expressed it, it was unnatural to go so long without urinating. Over a liter of clear urine was drawn with the catheter.

According to my experience the partial retention of tabes differs from that due to mechanical obstruction in one essential particular; in the latter case the amount of residual urine is constant while in tabes the amount varies from time to time within rather wide limits, from almost nothing to several hundred cubic centimeters. In old long-standing cases in which infection of the bladder has occurred the symptoms are greatly aggravated and incontinence is apt to be a prominent symptom. The constant dribbling of foul, alkaline urine renders the condition of these poor unfortunates well-nigh intolerable. In such cases the bladder rarely empties itself and the residual pool of infected, decomposing urine increases the discomfort of these miserable patients.

In a large percentage of early cases cystoscopy shows certain characteristic changes in the bladder cavity associated with the disturbance in function. These changes in the tabetic bladder are so constant and characteristic that the diagnosis is frequently made by the urologist, oftentimes long before other symptoms of the cord lesion are in evidence. Examination reveals a varying amount of vesical retention without demonstrable mechanical obstruction. Cystoscopy will show the following changes: (1) trabeculation, (2) relaxation of the vesical outlet, (3) elevation and hypertrophy of the trigone.

Fig. 116. Fig. 117.

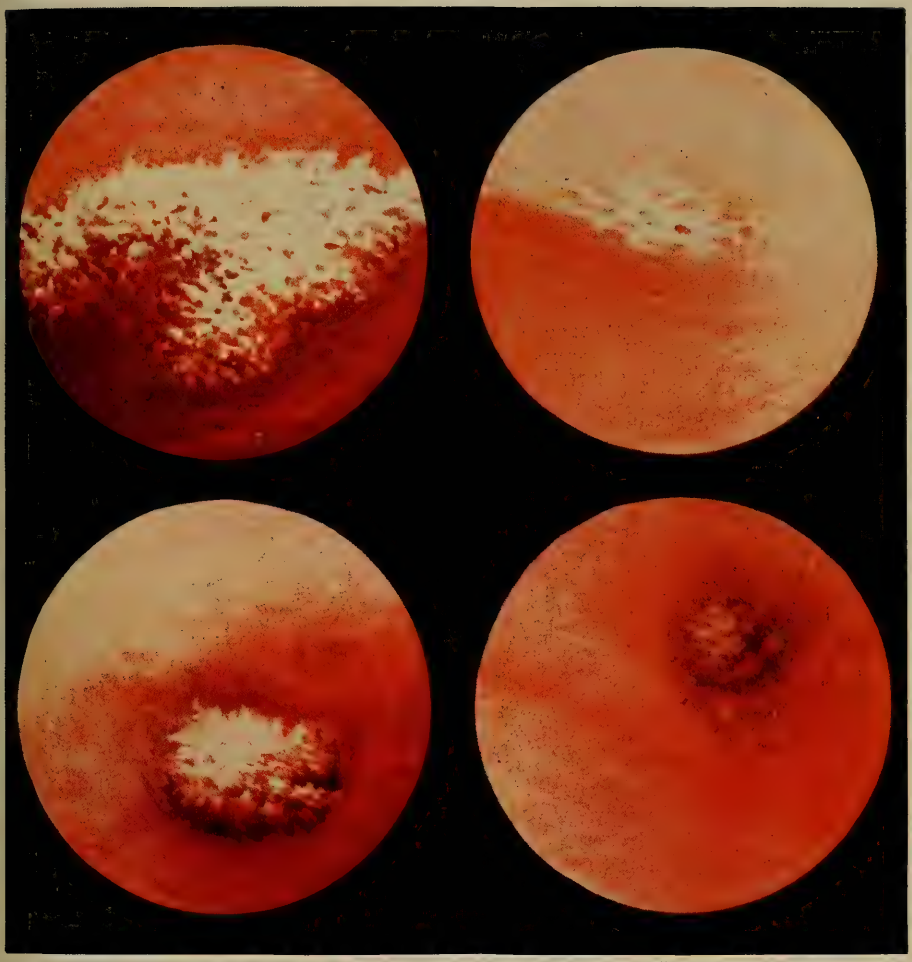

Fig. 118. Fig. 119.

TERTIARY SYPHILIS OF THE BLADDER

Fig. 116.—Syphilitic ulcer with incrustation situated at the left ureteral opening. Female, age forty-nine, with myelitis syphilitica. Six ulcers of varying size scattered over the bladder. Bladder normal after two months' antisyphilitic treatment combined with bladder irrigations.

Fig. 117.—Scar following treatment of lesion shown in Fig. 116.

Fig. 118.—Ulcerating gumma below the right ureteral orifice. Female, sixty years. For six months hematuria, frequency, and pain. Bladder normal except for ulcer. Infection twenty years before. Rapid healing under mercury.

Fig. 119.—Ulcerating gumma at the right ureteral orifice. Male, age forty-six years. Syphilis fifteen years before. Intermittent hematuria for three months. Disappearance of lesion after thirty injections of mercury.

(From Englemann: Folia Urologica, v, No. 7, p. 478.)

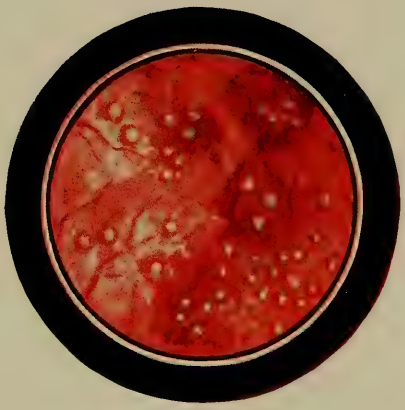

Fig. 120.

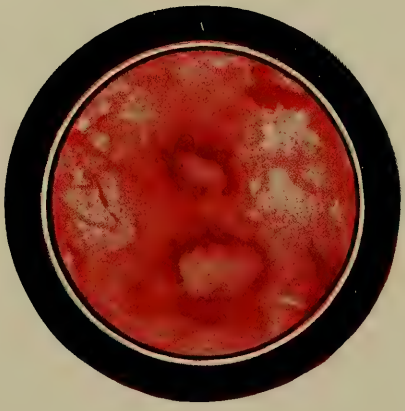

Fig. 121.

Tertiary Syphilitic Lesions of the Bladder

Fig. 120.—Female, age thirty-nine years. Profuse intermittent hematuria for five years. Mixed treatment.

Fig. 121.—Same patient after treatment.

(From Michailoff: Ztschr. f. Urologie, 1912, p. 216.)

Trabeculation of the bladder, Balkenblase, is the most constant intravesical change associated with tabes. These trabeculæ are composed of a fine interlacing network of muscle bundles and are particularly well marked at the base and on either side of the trigone. They not infrequently extend high up laterally and may involve the entire bladder wall. The trigone is never involved. The texture of this trabeculation is peculiarly fine and delicate in marked contrast to the coarse trabeculæ observed in prostatic obstruction.

Relaxation of the internal sphincter is another important sign of disturbed innervation. In extreme cases the prostatic urethra forms a pouch distended with urine and communicating freely with the bladder cavity, through a window formed by the relaxed atonic vesical sphincter. In such a case it is possible to inspect the prostatic urethra with a Nitze cystoscope by withdrawing the instrument into the prostatic urethra. Attention was called to this point by the writer in reporting an observation of this kind in 1912 (Trans. of the Am. Assn. of Genito-urinary Surgeons, vol. vii, p. 187; 1912). In passing a catheter the urine begins to escape as soon as the eye passes the cut-off muscle.

The trigone is often elevated and thickened. It is necessary to markedly depress the ocular end of the cystoscope to keep the lens off the surface of the trigone. The interureteral bar is elevated, prominent, and behind this there is a distinct pouching of the bladder wall.

In late stages after infection has taken place the changes occurring in ordinary cystitis are added to those just described and these help to confuse the clinical picture.

It is very important to differentiate between the retention of tabes and that due to obstruction at the vesical outlet. This is necessary in order to avoid the mistake of operating for the relief of supposed mechanical obstruction when the retention is really the result of a nerve lesion. It is to be remembered that the two conditions may coexist, but this is unusual.

Treatment.—The bladder involvement in parasyphilitic diseases is little influenced by the administration of mercury and iodide of potassium. Arsphenamine used intravenously or given into the muscles is of little value. The best results are obtained by the intraspinal injection of arsphenaminized serum, following

the Swift-Ellis technic. By this treatment further progress of the disease may be arrested and improvement in bladder function obtained. In early favorable cases before extensive nerve degeneration has occurred the best results are seen. Hence the earlier diagnosis is established and treatment begun, the better the results will be.

In long-standing cases with infection of the bladder, the type of case usually considered hopeless and helpless, very decided improvement may be obtained by the above measures coupled with regular catheterization and patient, intelligent, long-continued local treatment of the bladder.

SYPHILIS OF THE PROSTATE

The prostate is rarely involved in syphilis. In common with the bladder it appears to enjoy a relative immunity to infection in this disease. It is difficult to understand why this is so, especially as the testicle which is so closely related anatomically is frequently attacked. The reports of a small number of cases in recent literature indicate, contrary to the belief of earlier writers, not only that syphilis of the prostate undoubtedly does occur, but also that this may be by no means as rare as we have been led to believe.

In 1851 Ricord[31] reported two cases of syphilis of the prostate both of which came to autopsy. These are probably the first cases recorded in literature and the only cases which have been studied postmortem. The cases reported by Reliquet,[32] Rochon,[33] and Grosglik[34] are generally referred to by subsequent writers. More recently cases have been reported by Desnos,[35] Hesse, Cook,[36] Wright,[37] and Ulrich.[38] In addition to these one finds a certain number of cases of syphilis of the bladder in which the prostate was also involved (Le Fur, Margoulies, Duhot, Frank).

The disease occurs most frequently between the ages of thirty and fifty years. The youngest patient was twenty-eight years old (Reliquet). The lesions develop during the tertiary period, years after the primary infection. This interval varies widely in the cases reported.

Rectal examination discloses a greatly enlarged, indurated

prostate with an irregular, nodular surface. The enlargement is not uniform; the right lobe is most frequently involved. The induration may extend high up over the bladder wall, and the rectum may be adherent (Desnos). By reason of the hard, cartilaginous consistence, and the irregular, nodular surface, the condition is usually confused with malignant disease. These changes are probably due to gummous deposits within the gland surrounded by dense fibrous tissue, sclerogummous lesions.

Symptomatology.—There are no characteristic signs or symptoms of syphilitic prostatitis by which this can be differentiated from the ordinary chronic forms of infection. The symptoms are often those of a mild chronic posterior urethritis—slight discharge with shreddy urine, and moderate discomfort referred to the perineum and along the urethra. There is often a history of an ancient gonorrhea and the symptoms are usually referred to the previous urethral inflammation. The case recorded by Hesse is unusual in that there was no history or evidence of gonorrheal infection. There was marked frequency, thirty to forty times at night. The urine was clear and free from cellular elements and the secretion obtained by massage of the gland was practically normal. The prostate was enlarged, hard with a circumscribed swelling the size of a hazelnut in the right lobe. The Wassermann test was positive. The condition cleared up completely with two weeks of intense antiluetic treatment including arsphenamine and without any local treatment.

Diagnosis.—The condition is usually not recognized at first and is confused with chronic prostatitis (Desnos), or more often malignant disease (Desnos, Cook, Hesse). The first observation of Desnos is interesting as the diagnosis of chronic prostatitis was first made. Later the condition was thought to be malignant disease. Under potassium iodide the symptoms subsided and the prostate returned to normal in five weeks. Desnos emphasized the importance of extensive induration extending well up above the prostate and the immobility of the rectal wall as diagnostic points of great value. The adhesion of the rectal wall to the enlarged, nodular prostate led to the correct diagnosis in his second case.

It is important to recognize the fact that gumma of the prostate, though rare, does occur. The history or the presence of

the Swift-Ellis technic. By this treatment further progress of the disease may be arrested and improvement in bladder function obtained. In early favorable cases before extensive nerve degeneration has occurred the best results are seen. Hence the earlier diagnosis is established and treatment begun, the better the results will be.

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It is important to recognize the fact that gumma of the prostate, though rare, does occur. The history or the presence of

syphilitic infection in a patient between the ages of thirty and fifty years, presenting symptoms of chronic prostatitis should arouse suspicions, especially if the gland is markedly irregular, hard, and the enlargement is greater than is generally observed in chronic prostatitis. The Wassermann test is of very great value in doubtful cases. And finally the diagnosis is confirmed by the results of antiluetic treatment. The therapeutic test serves to differentiate the syphilitic from the common forms of prostatitis. Local treatment by massage and irrigations not only does not relieve symptoms, but generally aggravates the condition. Under specific treatment alone the symptoms rapidly subside. The therapeutic test is also an important aid in differentiating syphilis from malignant disease. When there is any question as to the diagnosis, one should give a course of potassium iodide.

In all the recorded cases except two (Ricord) the diagnosis was based upon the clinical data alone. As these patients all got well, there was no opportunity for pathologic and histologic study. Desnos has questioned the diagnosis in the two cases of Ricord, and considered the lesions tuberculous. In no case so far recorded, therefore, is the diagnosis absolutely certain, since pathologic and bacteriologic proof is lacking. However, in no disease has the result of treatment so great a diagnostic value as in syphilis. The finding of treponemata associated with these lesions would definitely establish the diagnosis. Up to the present time this has not been done.

Treatment.—Local treatment is useless. Antiluetic treatment should be employed and pushed vigorously. Potassium iodide should be given in large doses. This may be combined with intramuscular injections of mercury. Under intensive mixed treatment alone the condition will clear up in three to five weeks. Arsphenamine should be used to secure, if possible, a persistent negative Wassermann reaction.

SYPHILIS OF THE SPERMATIC CORD

Syphilitic affection of the spermatic cord is rare and generally occurs in association with syphilitic orchitis and epididymitis. Still more rarely the spermatic cord alone is involved and

is the seat of a gummous deposit. A few undoubted cases of this kind have been reported. The literature has been reviewed by Campbell[39] in connection with the report of his case.

The cord may be involved in a diffuse funiculitis. It is then decidedly thickened, indurated, and fused with the surrounding tissues. Reclus reports two cases in which the vasa deferentia were as stiff and rigid as a glass rod and attained the size of a pen holder.

More commonly one palpates a nodular swelling along the course of the cord between the epididymis and the external ring. In size this tumor varies from an almond to a goose egg. In the case recorded by Verneuil there was a gummous swelling the size of two fists occupying the scrotum and extending along the cord as far as the iliac fossa. During life this was thought to be a carcinoma. The tumor is generally sharply defined, single, and unilateral (Goldenberg,[40] Mauriac, Morrow, Campbell). At times the nodules are multiple (Kocher, Lancereaux), and bilateral (Bert). They are generally round or oval in shape, intimately connected with the cord, and often fused with the surrounding tissues. Pain, either spontaneous or due to pressure, is usually present. These nodules show little tendency to suppurate, although this may occur (von Zeissl).

The diagnosis is easily made where there are associated lesions of the testicle and epididymis. In the rare cases where the spermatic cord alone is the seat of a gummous lesion the diagnosis is not so readily made. This must then be based upon a history of infection, a positive Wassermann, and most important of all, the therapeutic test.

The condition clears up readily under antisyphilitic treatment. The mixed treatment with mercury and potassium iodide has been followed by absorption and disappearance of the swelling in the cases reported. One should push intensive treatment until satisfied that the infection has been as completely removed as possible.

SYPHILIS OF THE TESTICLE AND EPIDIDYMIS

Syphilis of the testicle (syphilitic orchitis) is relatively common. Among 171 subjects of late acquired syphilis coming to

autopsy the testicles were involved in 39 per cent. The lesion was bilateral in 23 per cent (Symmers).[41] Clinical observation shows that syphilis attacks the testicles more frequently than any other part of the genitourinary tract.

The disease is usually primary in the testicle; the epididymis is involved secondarily. Just the opposite occurs in tuberculous disease; the primary focus is almost invaribly situated in the epididymis, and the process in the testicle is secondary.

The lesions are observed at any period of the disease, usually during the first four years, though cases occurring as early as two months and as late as thirty-one years have been recorded. Hydrocele is a frequent accompaniment.

Syphilitic Epididymitis

Primary syphilitic epididymitis without involvement of the testicle is rare, but does undoubtedly occur. The French have recorded numerous observations of syphilitic epididymitis occurring during the secondary stage, following the publication of Dron in 1863. These have not been generally accepted by German authors, but a few cases have been reported (Pinner, Rosenthal), and von Zeissl has given a good clinical description of the affection in his textbook. Very few reports have appeared in American literature.

The earliest appearance of epididymitis after infection is two months. It appears more frequently between one and five years. Two forms of the disease have been observed: (a) a subacute or chronic epididymitis occurring in the late secondary or early tertiary stage. This is sometimes bilateral. The globus major is chiefly affected, but the process may extend to the body, tail and even into the vas (Wright's cases).[42] The swelling is gradual, progressive, and for the most part painless. At first smooth and elastic, this becomes irregular, nodular and very hard or cartilaginous as the disease progresses. Effusion into the tunica vaginalis takes place forming a hydrocele which may interfere with palpation and renders the diagnosis obscure.

The course of the disease is essentially chronic. Acute development and the presence of subjective symptoms are rare. The patient's attention is often first directed to the condition by the gradual increase in the size and weight of the scrotum due

to the accompanying hydrocele. On palpation one feels a hard, indurated, nodular globus major with a characteristic sharp edge which caps the testicle like a helmet. Less frequently the process extends to the body and tail of the epididymis. A distinct sulcus separates the enlarged epididymis from the testicle. There is little or no sensitiveness on pressure. The testicle is not involved and the vas is normal.

Exceptionally the onset may be more acute. There is spontaneous pain in the sensitive, swollen epididymis, radiating along the cord. This is increased with the slightest movement. These acute symptoms subside in a few days and the course of the disease becomes subacute or chronic.

(b) Small gummata may occur in the epididymis in the tertiary stage. They appear as hard, indurated nodules, confined to the epididymis. When the whole organ is involved gummatous deposits will often be found along the cord of the same side. These show little tendency to break down. This condition resembles tuberculous infection with which it is easily confused.

Syphilitic Orchitis

Syphilis of the testicle occurs during the tertiary stage of the disease, most commonly during the first four years. After the skin and subcutaneous tissue and the bones, the testicle is the most frequent seat of tertiary syphilis (White and Martin). It may develop during the presence of other active syphilitic lesions, or the disease of the testicle may be the only manifestation of syphilis.

Two forms of the affection are recognized: a diffuse interstitial sclerosis which is the most common form, and gumma of the testicle. These two forms are rarely distinct. The two processes, interstitial sclerosis and gummatous infiltration, usually occur together and give rise to the familiar sclerogummous process so frequently seen in tertiary syphilitic lesions.

In diffuse interstitial orchitis infiltration and sclerosis of the interstitial tissue predominates. The tunica albuginea is thickened, and the infiltration extends to the connective-tissue framework which becomes dense and firm. Contraction of the newly formed connective tissue results in atrophy of the testicle, either

partial or complete. On section the testicle is dense and firm and in the later stages may be very hard. Dense bands of connective tissue radiate from the thickened albuginea and constrict the glandular structure. There is often a small amount of fluid in the tunica vaginalis. This is rarely large. Absorption of this hydrocele fluid may be followed by adhesions between the two layers of the tunica vaginalis and obliteration of the cavity.

Gumma of the testicle is much less common than is generally supposed. In the series of autopsy cases reported by Symmers not a single case of gumma of the testicle was encountered. The same experience is reported by other pathologists. Gummata usually develop in a testicle already the seat of a diffuse or partial interstitial orchitis. The affection is characterized by the development of one or more small, hard, or elastic nodules which gradually increase in size. These nodules are surrounded by a dense fibrous capsule by which they are sharply delimited from the surrounding tissue. A large gumma may break down, become adherent to the overlying skin, break through and discharge necrotic material. A deep ulcer with a sloughing, necrotic base results.

Course.—Syphilis of the testicle is insidious in onset, extremely slow in development, and gives rise to few subjective symptoms. Its presence is usually detected by the gradual increase in size and weight of the scrotum. It is for this enlargement that the patient usually seeks relief.

Exceptionally the symptoms may be more acute. The swelling of the testicle develops rapidly. It is exquisitely tender on palpation, the overlying skin is reddened and edematous, and there may be acute pain radiating along the cord. In addition to local heat the temperature may rise to 103°. The condition is likely to be confused with gonorrheal epididymitis as happened in one of my cases.

Diagnosis.—The diagnosis is usually simple; it may be extremely difficult. A history of lues will suggest the character of the enlargement. It must be remembered, however, that a negative history does not exclude syphilis. This can not be emphasized too strongly. The character of the swelling is important. The testicle itself is involved in the swelling which is

smooth or nodular and which preserves the outline of the testicle. It is very hard with a wooden feel and is very heavy. There is no tenderness on palpation and subjective symptoms are slight or absent altogether. Testicular sensation is lost. The small hydrocele usually present forms a relatively thin layer of fluid covering the anterior surface of the tumor.

Syphilis of the testicle must be differentiated from tuberculous disease, gonorrheal epididymitis, hematocele, and new growth.

In tuberculous disease the primary focus is in the epididymis, chiefly the globus major, which is enlarged, infiltrated, and nodular. The vas is often thickened and nodular. The overlying skin becomes adherent and fistulization occurs relatively early with the discharge of the characteristic thin tuberculous material. In such cases we can always trace the fistulous tract directly to the epididymis while in syphilis the fistulous tracts extend to and communicate with the testicle proper. In tuberculous infection associated lesions of the prostate, seminal vesicles, or bladder may be in evidence. The subjective symptoms and local signs are always more marked.

There should be no difficulty in differentiating gonorrheal epididymitis. Confusion arises only in the exceptional cases of acute syphilitic orchitis. And here a careful history together with the absence of other evidence of urethral infection will lead to a correct diagnosis.

The greatest difficulty is experienced in differentiating cases of syphilis and tumor of the testicle. It may be quite impossible to distinguish these two conditions by the local examination alone. The history of the case, the presence of enlarged inguinal glands, and the more rapid development of new growth may give the clue. The Wassermann test is often helpful. In case of doubt one should appeal to the therapeutic test. It should be an inflexible rule in every case of suspected tumor of the testicle to place the patient on intensive antiluetic treatment for a period of at least two weeks and examine carefully for any change in the size of the swelling before resorting to the removal of the growth. If there is an appreciable diminution in the circumference of the scrotum we may be sure that the condition is syphilitic and not new growth. Finally an exploratory in-

cision may be necessary to clear up the diagnosis. In the case of new growth numerous dilated veins coursing over the surface of the mass establishes at once the diagnosis of malignancy.

Prognosis.—The prognosis in general is good. Atrophy results from the excessive development and contraction of connective tissue in neglected cases. But where the glandular structure has not been destroyed this will continue to functionate when the process has been arrested by appropriate treatment.

Treatment.—As syphilis of the testicle responds promptly to antiluetic treatment this should be pushed vigorously. The patient should be warned that the affected testicle may be smaller than normal following treatment and that the longer treatment is delayed the greater the chances of losing completely the function.

SYPHILIS OF THE FEMALE GENITAL ORGANS

History.—Ambroïse Paré (1510-1590) was probably the first to study syphilitic lesions of the female genitals. Astruc[43] in 1736 published the first comprehensive article on the subject. Lancereaux,[44] Fournier,[45] Neumann[46] and Herxheimer[47] have made extensive contributions. Within the past year Gellhorn and Ehrenfest[48] have collected practically all of the cases from the literature and have published a most exhaustive paper, a paper to which the author is indebted for most of the following description. It is of interest to note that many of the most important contributions have come from the pens of dermatologists.

Lesions of the Vulva

Chancre of the vulva has already been described, but perhaps it would not be amiss to again call attention to the fact that a considerable amount of edema frequently accompanies a chancre upon one of the labia majora. Of the secondary lesions, condylomata are much the most frequent, and practically the whole surface of the labia may be converted into condylomatous masses, which at times assume a hypertrophic aspect. Ravogli[49] has called attention to frequency of true venereal warts, due to the irritating discharge from syphilitic lesions. True gummous lesions are not common, but are occasionally found. Special interest attaches to the so-called "esthiomene," because of the

discussion that has been waged concerning it, some men holding that it was syphilitic and some that it was due to lupus or some other type of chronic infection. By esthiomene is meant the condition that sometimes arises in a dissolute and careless type of woman where there is a brawny, chronic, inflammatory, generalized infiltrate, sometimes associated with ulceration. Hyde[50] and Taylor[51] believe that this condition is due to syphilis alone. More recently Taylor[52] has again described this condition, calling it "late indurating edema," and has pointed out that as sequelæ there may arise general atrophy with deformity, a condition similar to that of kraurosis vulvæ, epithelioma, chronic cellular hyperplasia, elephantiasis, gangrene and phagedena.

Lesions of the Vagina

Because of the resistance of the mucous membrane of the vagina, and also because of the character of the secretions, chancre of the vagina is exceedingly rare. Cases have been reported by Mauriac,[53] Glueck,[54] Bockhart,[55] Neumann, Rille,[56] who recorded twenty-one instances (!), Bobrie[57] and Nielsen.[58] As a rule the chancre is small, but may attain a diameter of 2 cm. Typical changes in the inguinal glands occur only when the primary lesion is situated in the lower portion of the canal; when it is higher up the pelvic glands enlarge. But little scarring is left.

Secondary lesions of the vagina are very rare. Cases have been reported by Fournier, Neumann, Oppenheim,[59] Balzer[60] and Rille. The lesions may appear either as macules or papules; the latter may either become hypertrophic or ulcerative. These lesions give no symptoms, hence are not found unless searched for.

Late lesions but rarely originate in the vagina. When found there, they usually have their starting place in either the vulva or the uterus. Cases have been reported by Birch-Hirschfeld,[61] Winckel,[62] Neumann, Verchère,[63] Spinelli,[64] and Oppenheim, but Gellhorn and Ehrenfest state several of these can not be accepted as authentic.

Lesions of the Cervix

Gosselin[65] in 1843 was one of the first to call attention to chancre of the cervix. Bennett[66] and Behrend[67] were other early writers on the subject. Fournier emphasized their importance

in 1873. Mrazek[68] in 1881 published a valuable article. In 1904 Rille published an account of 160 cases (!). Other late reports are those of Moraller,[69] Ivens,[70] Falk,[71] Neisser,[72] and Wile and Senear.[73] The frequency of initial lesions upon the cervix is given by various observers as from 1 to 15 per cent of all chancres occurring in women. Women who have borne children are most apt to develop cervical chancres, probably because of lacerations and erosions. The anterior lip is rather more often affected than is the posterior, and multiplicity is not uncommon. As a rule the diameter is about 1 cm. In general they correspond with the types of genital chancre already described. When healed they leave but little scar formation. Several authors have mentioned the fact that in case of pregnancy the ulcers may heal very slowly. In exceptional instances a considerable amount of cervical rigidity may remain as an aftermath.

Secondary lesions are probably more common than the rather scanty literature would seem to indicate. Articles upon the subject have been written by Fournier, Mrazek, Rille, Oppenheim, Rode[74] and Pinkuss.[75] Recently Gellhorn and Ehrenfest have reported eight cases. The lesions first appear as macules, which usually come to resemble mucous patches in the mouth. At times distinct papules form, and true condylomata lata have been reported. Rarely there may be ulceration. The macules and papules give no symptoms, while from ulcers there may be considerable discharge.

The first reference to tertiary lesions of the cervix is to be found in the work of Astruc (1775). Then followed the accounts of Lagneau[76] and Duparcque.[77] Morris[78] and Otis[79] of America were among the early authors to describe such cases. However, as late as 1908 Oppenheim stated that but little was known concerning gumma of the cervix. Gellhorn and Ehrenfest have collected twenty-one cases from the literature and have added five cases of their own. The process may extend into either the uterus or the vagina. In appearance it is characteristic of gummous processes in other portions of the body.

Lesions of the Uterine Body

Chancre of the endometrium has never been observed although it is theoretically possible, nor is there any evidence of secondary

lesions. Hoffmann[80] has reported the one authentic case of gumma of the endometrium. Several cases of gummata of the muscular body have been described, the latest by Norris,[81] who states that there are two types of gummata, one where there is a diffuse infiltration, and the second where there is one localized lesion. Other papers have been written by Recasens[82] and Franceschini.[83]

Lesions of the Fallopian Tubes

The best known case of tubal syphilis that is to be found in the literature is that of Bouchard and Lepine,[84] which Gellhorn and Ehrenfest do not accept as authentic. Wassilief[85] claims that syphilitic salpingitis occurs in two forms, the first congestive and the second sclerotic. He further states that in the first form there is a characteristic blue color. However, Gellhorn and Ehrenfest can not accept all of his cases as conclusive, and point out that the blue color may be found in other conditions. No one has as yet demonstrated treponemata in the tubes in a case of acquired syphilis.

Lesions of the Ovaries

Simple enlargement, syphilitic oophoritis, tertiary sclerosis, and true gummous formation have been described, but the authors have furnished but little real proof of these lesions being of a syphilitic nature according to Gellhorn and Ehrenfest. While amenorrhea is common in syphilis and is frequently relieved by antisyphilitic treatment, this is no proof of syphilitic changes in the ovaries. This paucity of cases is all the more surprising when we consider how frequently the testicle is invaded by the treponema. However, I have seen one case where an enlarged ovary was removed at operation, and where histological examination gave proof positive that it was a true caseating gumma. Modern literature on the subject has been written by Virchow,[86] Meyer,[87] Ozenne,[88] Dalché and Fouquet,[89] Meirowsky and Frankenstein[91] and by Wagon.[92]

Lesions of the Breast

At the present time chancres of the breast are rather uncommon, but still they do occur. Cole[92] has recently reported a case

where there was a chancre upon each nipple. I have seen one case in a woman, whose lover had a mucous patch upon the lip. When wet nursing was in vogue, there were many instances where a syphilitic child was responsible for the infection. The figures of Bulkley and Fournier, already quoted in the chapter upon the Chancre, show how prevalent these chancres formerly were.

White and Martin,[93] as well as other authors, state that during the early eruptive period there may occur an acute mastitis, with diffuse swelling and pain; this may be either unilateral or bilateral. It is analogous to the swelling that may occur in the thyroid or the salivary glands at the same period.

Sauvages[94] was probably the first to recognize the late manifestations of mammary syphilis. Probably the commonest form is the localized gumma, examples of which have been described by Power,[95] Bryant,[96] Sheild[97] and others. Usually the lump breaks down rather rapidly, and this point will serve to exclude cancer. Also the neighboring glands but rarely become enlarged, which, by the way, is not a point of any great value in differential diagnosis. It may be very difficult to exclude chronic mastitis or tuberculosis except by laboratory tests, or the finding of other signs of lues.

The second form of mammary syphilis is the rare, diffuse syphilitic infiltration, which is due to miliary gummata, and which is analogous to the condition occurring in so many of the internal glandular organs. Ambrosoli[98] has reported two cases.

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[26]Michailoff, N. A.: Syphilis der Harnblase und der oberen Harnwege, Ztschr. f. Urol., 1912, vi, 215.
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[42]Wright: Urol. and Cutan. Rev., December, 1916.

Syphilis of the Female Genital Organs

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[45]Fournier: Leçons cliniques sur la Syphilis, Paris, 1881.

is probable that in the future it will be found that endocrinology will be recognized as but a branch of vegetative neurology.

Bibliographies concerning the general subject of endocrine gland disease and functions may be found in the works of Barker,[1] Biedl,[2] Falta,[3] and Schäfer.[4]

Syphilis of the Thyroid Gland

The thyroid gland is supposed to have the following functions: it controls iodine metabolism; it controls the intracellular protein metabolism, its action being general, and its oversecretion emphasizing normal activity of all tissues; it is closely allied with the vegetative nervous system; the thyroid autocoid augments the effect of adrenalin simultaneously placed in the circulation, and may be found to augment the action of other autocoids.

There are two different types of hypersecretion, the sympathicotonic and the vagotonic. In the former there is well marked exophthalmos, marked tachycardia, dry skin, falling hair and alimentary glycosuria, while in the latter there is no exophthalmos, but slight tachycardia, and marked palpitation, sweats, hyperacidity of the stomach, diarrhea and unlessened carbohydrate tolerance. The two groups also show very different eye signs, for in the former, there is a negative von Graefe (dissociation between the movements of the upper lid and of the eyeball), positive Loewi (epinephrin mydriasis) and a positive Moebius (insufficiency of convergence), while in the latter the von Graefe is positive and the Moebius negative.

There is but little literature as to hyperthyroidism caused by syphilis, but it undoubtedly can occur in early syphilis, for we all know that infections may cause a temporary oversecretion. Levy-Franckel[5] reports eighteen cases of Graves' disease that developed late in the course of the secondaries. Thompson[6] states: "According to Gougerot, three cases with symptoms of exophthalmic goiter which were improved by antisyphilitic treatment have been reported by Penzold." Poncet and Leriche[7] have recorded a case in a syphilitic woman who developed symptoms of hyperthyroidism, and who was cured by arsphenamine. Clark[8] has also reported a case in a congenital syphilitic (see section on Congenital Syphilis). Finally Thompson[6] has very

recently reported still another case in a man of seventy-two, who showed a pulse rate of 140, and protrusion of the eyeballs as well as a definite gumma of the thyroid. Under antisyphilitic treatment all of these manifestations cleared up. I have seen one case of vagotonic hyperthyroidism in a woman suffering from cerebrospinal syphilis, which entirely disappeared under antisyphilitic treatment. In another instance a young negro girl came to the dispensary because of secondary syphilis. After she had been under treatment for some time (she received no iodides) she developed a large general swelling of the thyroid, and some signs of vagotonic hyperthyroidism. She was referred to Dr. Reede, who told me that she had previously had a mild Graves' disease. One would naturally think that gummous formation where there is a destruction of tissue would cause undersecretion, but this was not the case in either Clark's or Thompson's patient. It would seem that perhaps syphilitic changes in one portion of the gland may stimulate the remainder to oversecretion.

In conditions of hypothyroidism the gland can usually not be felt, the skin is thickened and dry, there may be supraclavicular fat pads, the face lacks expression, all of the metabolic processes are slowed, the temperature is frequently subnormal, constipation is the rule, and there is evident lack of memory and slowness of thought.

There is very little literature as to the part that syphilis can play in causing hypothyroidism, however, one can not help feeling that if an interstitial thyroiditis exists, as occurs in practically all other organs, there should be some symptoms. As bearing upon this point Kohler[9] has reported a case where a woman of forty-eight had a tumor of the thyroid that disappeared under iodides: a concomitant myxedema also disappeared. Pospelow[10] has also reported an instance where myxedema developing in an undoubted syphilitic was cured by antisyphilitic medication. More observations upon this point are much needed.

However, the literature does deal with three distinct types of lesions, the diffuse swelling of the gland associated with early syphilis, gumma formation, and disturbances caused by the administration of iodine.

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Engel-Reimers[11] has reported observations upon 250 cases of

syphilis. Of 152 females, 86 showed enlarged thyroids early in the course of the disease, while 44 out of 98 males were similarly affected. However, the presence of preexisting thyroid enlargement was not rigorously excluded, neither was any mention made as to type of treatment employed, that is, as to whether the iodides were administered. "The swelling appears in the secondary incubation period or concomitantly with the first constitutional symptoms. It does not appear to be influenced by antisyphilitic treatment, but, like the swelling of the lymph glands, disappears gradually in the course of a year or two." Engel-Reimers described the enlargement as being confined to the lateral lobes, and as being soft and painless. Mauriac,[12] Lockwood,[13] Julien and others have described this condition. I am convinced that it is not common, for I have encountered but three cases in a large series where it was carefully searched for. In one of these cases later search revealed the fact that there had been a goiter of long standing that suddenly became much enlarged after the appearance of the secondary lesions, although no iodides had been employed. Davis[14] mentions the fact that the swelling may be hard and painful.

A number of cases of gumma of the thyroid have been reported. Davis[14] has collected all of the cases up to 1910, in addition to reporting one of his own, and more recently Thompson[6] has again reviewed the literature. The other case reports were by Wagner,[15] Ziegler,[16] Fraenkel,[17] Mendel,[18] Thursfield,[19] Clarke,[20] Lancereaux,[21] Power,[22] and Poncet and Leriche.[7] The tumor is usually painless, may be either large or small, may or may not ulcerate, and may cause any of the usual pressure symptoms. The histology of the condition is identical with that of gummata in general. On the whole antisyphilitic treatment has been successful.

In 1906 Mendel suggested that some of the so-called cases of thyroid syphilis might be merely examples of iodine thyroiditis. He felt that most of the early cases were of this nature. This view has escaped the general attention that it deserves, in spite of the fact that symptoms of hyperthyroidism may be caused by large doses of the iodides.

Other articles dealing with syphilitic thyroiditis are those of Hülth,[23] Shiron,[24] Rosenbauer[25] and Zoeller,[26] who gives an admirable historical review.

Syphilis of the Parathyroids

We are fairly well informed concerning the functions of the parathyroid glands, knowing that they control the calcium metabolism of the body, and that a lack of their secretion results in tetany, or in paroxysmal contractions of the muscles, paresthesias and trophic disturbances.

Concerning the overfunction of these glands the literature is silent. I can find no references concerning syphilitic lesions of the parathyroids, and yet it is reasonable to infer that some of the above-mentioned phenomena might be due to luetic lesions.

Syphilis of the Thymus

The functions of the thymus are as yet not perfectly understood, as Reede[27] has well pointed out. Normally the gland is supposed to involute soon after puberty, but this is by no means always the case. Our knowledge of underfunction of the gland is very incomplete as the experimental evidence is conflicting, and as the clinical evidence has never been carefully correlated. Overfunction is supposed to result in the so-called status thymicus. Certain it is that the gland has to do with the development of the body. The literature contains a number of references to congenital syphilis of the thymus, but there are no cases of acquired lues of this gland upon record.

Syphilis of the Pineal Gland

Irritative lesions of the pineal body delay puberty, while destructive lesions cause precocious puberty. Tumors of the gland produce symptoms of increased intercranial pressure, certain focal manifestations, and some signs of disturbed internal secretions, chiefly premature puberty and changes in the carbohydrate tolerance. Concerning syphilis of the gland we are totally ignorant.

Syphilis of the Pancreas

This subject has already been discussed.

Syphilis of the Testes and Ovaries

This subject has likewise been discussed.

Syphilis of the Suprarenals

Irritative lesions of the medulla of the adrenals, causing oversecretion result in rapid pulse, increase in the blood sugar, increased blood pressure, shortened coagulation time, and irritability of the vasomotor system. Destructive lesions of the medulla naturally cause an opposite set of symptoms, namely, cyanosis, and sometimes heart failure. At this point it is interesting to note that it has been experimentally shown that arsenic and arsenic compounds may have a destructive action upon the medulla.[28]

Irritative lesions of the cortex produce the syndrome of suprarenal virilism, while destructive lesions produce Addison's disease, with its low blood pressure, weakness and pigmentation.

The low blood pressure, usually believed to be one of the symptoms of Addison's disease, is now believed by some of our best observers to be entirely due to weakness, and not to a primary change in adrenal secretion. There have been autopsies upon a number of cases which showed the classical pathologic findings of Addison's disease and in which a low blood pressure had never been observed.

Pathologists now recognize that syphilis of the adrenals, in the form of areas of round-celled infiltration, is very frequently found in autopsies upon patients dying of syphilis. Warthin[29] is very emphatic upon this point.

But little is known of the effect of secondary syphilis upon the adrenals. Various men have attributed the asthenia sometimes seen at this stage of the infection to changes in the adrenals, and Giuranna[30] has described changes in the cells, a finding that Sézany[31] was unable to confirm in autopsies upon three cases. However, in the late stages of syphilis a few cases of Addison's disease have been reported, one by Thompson[32] and another by Schaffner and Howard.[33] Addison's disease due to syphilis is probably commoner than has been believed.

Further information may be found in the writings of Jacquet and Sézary,[34] and Ribadeau-Dumas and Patii.[35]

Syphilis of the Pituitary

The pituitary body consists of three portions, the anterior glandular part, a posterior nervous part, and an intermediate portion. Each has special functions. Irritative lesions of the anterior lobe stimulate the general growth of the body, a condition spoken of as acromegaly, and an abnormal development of sex growth and function. Destructive lesions inhibit growth and likewise sex growth and development.

Some of the late work would seem to show that the posterior pituitary body has no separate functions and that the changes which were attributed to disease of this portion of the gland must be assigned to dysfunction of the whole gland.

A considerable number of cases of gumma of the pituitary have been described, most of them in women, curiously enough. In many of the cases there was no clinical history, the patient having died soon after admission to the hospital, or the lesions having been found at autopsy. The symptoms to be expected would naturally be those of increased internal pressure, focal symptoms due to local pressure, and those due to lack of function.

In the cases reported by Stroebe[36] and Turner[37] the disease was very acute, death resulting in six weeks. Semicomatose attacks seem to be the outstanding feature. Other observers have reported polyuria, tremors, and amenorrhea. Cases have been reported by Sokoloff,[38] Birsch-Hirschfeld,[39] Cushing,[40] Wagner,[41] Weigert,[42] Barbacchi,[43] Trosier,[44] Beadles,[45] Hektoen,[46] Rebandi,[47] Bianchi,[48] Hunter,[49] Woodley,[50] and Barker.[51]

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CHAPTER XVII

SYPHILIS OF THE NERVOUS SYSTEM

By John E. Lind,* M.D., Washington, D. C.

History.—Whether or not syphilis was known before the New World was discovered is a question of great historical interest, but scarcely of practical value. Ancient Roman and Greek writers have described disease pictures which might be interpreted as luetic, and Biblical accounts of certain plagues are very suggestive of syphilis. Corlett [1] states that it undoubtedly existed in China and Japan in ancient times, being known in the Chu dynasty in 1122 B.C. to 314 B.C. It is thought then to have traveled to America by Behring Strait and was then carried by Columbus' sailors to Spain from where it spread rapidly through Europe. Monkmöller,[2] however, does not believe that any of the ancient writers, such as Aretaeus and Caelius, ever saw this disease, and Falk agrees with him.

Whatever may be the truth of the above question, certain it is that we only meet with accounts of nervous syphilis after the discovery of America. Thus in 1497, Leoncino described a hemiplegia due to syphilis. He was followed in 1503 by Joseph Grünbeck, in 1511 by Emser, and 1519 by Ulrich von Hutten, who also described syphilitic paralyses. Syphilitic meningitis was described in 1530 by Paracelsus, who was nearly three centuries ahead of his time in saying that all organs of the body were affected by this disease. He was inclined, however, to confuse gonorrhea with syphilis. Fracastorius (1521), who was godfather of the disease, does not mention involvement of the nervous system. Syphilitic neuralgias were described by Nicolaus Massa in 1556. Ten years later Borgarutius described neuralgias due to syphilitic involvement of the meninges. During the same decade Amatus Lusitanus referred to headache due to intracranial osteitis of syphilitic origin and Botalli thought that blindness might result from

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cerebral syphilis. The seventeenth century saw a great deal of literature about the interrelations of syphilis and the nervous system. The most important productions were those of Guarinoni, Vidus Vidius who described syphilitic epilepsy, and Thiery de Heury and Zechius who added syphilitic spasms. Zacutus Lusitanus discussed syphilitic blindness, and towards the close of the century Blagny wrote on pains due to syphilis.

General paresis was first brought to attention by Scholtzius in 1610, but Willis, in 1672, wrote the first authentic description of it as a clinical study. In fact, during the seventeenth century much was written about syphilis of the nervous system. Felix Plater, Rhodius, Ballen, and Cummius are especially mentioned by Astruc,[3] who has written the best review of this period. During the next century many other features of the subject were discussed; deafness, loss of smell, caries of the base of the skull, sciatica and psychoses. Sanché described syphilitic mania in 1777; before that amaurosis, facial palsy, leptomeningitis, and paraplegia due to myelitis had been discussed. About this time the study of the subject was seriously checked by John Hunter who excluded syphilis from the internal organs including the brain, in spite of the experience of the great epidemic at the end of the fifteenth century. Naturally, owing to his immense reputation, investigators were discouraged from studying the brain in syphilitic conditions, and it was only when Ricord was able to disprove this fallacy that the subject progressed again. Lallemand, in 1834, first demonstrated conclusively that syphilis of the meninges and brain substance did occur.

This brings us out of the dark ages of syphilis and the first figure we meet is that of Virchow[4] who in 1874 made extensive studies of vascular syphilis. Heubner[5] in 1874 and Alzheimer[6] in 1904 brought these to consummation. From Virchow to Schaudinn[7] there has been much work done, the most noteworthy being that of Nissl[8] and Alzheimer.

The modern era of the study of syphilis begins with Schaudinn who discovered the parasite in 1905 and was able to prove his contention although Doele[9] had probably seen it in 1892. Since that time it has been demonstrated in congenital syphilis of the nervous system, in syphilitic gumma of the brain and cord, in syphilitic meningitis, and in the cerebrospinal fluid. For a long

time its etiologic connection with paresis had been a moral certainty, but efforts to locate the treponema in paretic brains had failed. Then, in 1913, Noguchi and Moore[10] found and demonstrated it in paretic brains and to them goes the credit of this notable discovery. Finally Wassermann, Plaut,[11] Noguchi, Lange[12] and others perfected a serobiologic technic which makes it possible for us to diagnose accurately nearly all cases of nervous syphilis and thereby clear up many questions of prognosis, treatment, etc.

Frequency.—The frequency with which involvement of the central nervous system occurs in syphilis can only be a matter of conjecture. Any figures which are given at this stage must necessarily be below actuality, for while by means of our present diagnostic methods we are able definitely to say that such and such cases are syphilitic, there are many cases which for one reason or another are never subjected to these tests, and of whose exact nature we must consequently remain in ignorance. Nonne[13] reports 11,149 nervous patients seen in his private practice from 1892 to 1901 and from 1903 to 1907 and of these 173 had nervous syphilis, or 1.5 per cent. At Eppendorf Hospital, from 1892 to 1901 there were received in all 72,180 cases, of whom 282 had nervous syphilis or two-fifths of one per cent. From 1903 to 1907 Nonne saw 9936 nervous cases at his Eppendorf clinic and of these 104 were syphilitic; or slightly over 1 per cent. Hjelmann[14] states that brain syphilis develops in from fifteen to twenty-five of every 1000 cases of syphilis, or from 1.5 to 2 per cent. Reumont[15] thinks that about 8.5 per cent of all cases of syphilis are of the nervous system and he is supported by Englestedt and Gerhardt.[16] Mattauchek and Pilcz[17] give the following figures: Out of 4,134 paralytics, 195 were syphilitic, or 4.7 per cent; out of 3,430 syphilitics, 160 were paralytic, or 4.67 per cent. To give approximate figures, then, about .4 per cent of all medical cases have nervous syphilis, about 1.5 per cent of all nervous cases have syphilis and about 8 per cent of all syphilitic cases have involvement of the nervous system.

Etiology.—In considering the etiology, we must remember that probably about one-third of all cases of tertiary syphilis have no knowledge of having been infected. Along with a proved syphilis, too, there may be a toxemia of some other kind, chronic

alcoholism, or lead poisoning, or that from an infectious disease, or there may be a trauma, such as a blow on the head and these things may affect, directly or indirectly, the nervous system, complicating the picture. Alcohol especially must not be ignored, as alcoholism and syphilis are a frequent combination and very potent for evil. Chronic alcoholism has a debilitating effect on the central nervous system, and makes it an easier prey to syphilis. Oppenheim says too that where a syphilitic is non-alcoholic and for some reason indulges in alcoholic excesses he thereby facilitates the occurrence of brain syphilis. An injury to the head in luetics may cause an outbreak of brain syphilis.

The question of whether or not there is a special strain of syphilitic organism or variety of virus which has a predilection for the nervous system is still being debated. The supporters of the affirmative point out an analogy in the affinity of lead for the motor tracts of the cord and ergot for the posterior columns. Then, too, there are being observed an increasing number of cases of tabes and taboparesis in children whose parents had syphilis, but no tertiary symptoms. In many of these cases the etiologic factors of mental strains, excesses *aut in Baccho aut in venero*, and physical injuries, could be definitely excluded. Furthermore, it is a well-known fact that there are certain cases of syphilis which show recurrent skin affections and these cases do not develop nervous syphilis, while the nonoccurrence of skin eruption in patients who later show involvement of the nervous system has been proved by White.[18] Indeed it was partly responsible in the past for the failure to recognize syphilis, for example, as the indispensable factor in general paresis, for the patients were often not aware that they had ever had syphilis. Other arguments are the following: the frequency of conjugal tabes and other syphilogenetic diseases; general paresis in the husband, cerebrospinal syphilis in the wife, etc. Skorzynski reports a case where the father had brain syphilis and the mother and child paresis. Finally there are the cases where a number of nonrelated persons have been infected from the same source and have developed nervous syphilis. Nonne has collected 1902 such cases from the literature. The one most quoted is that of three friends who had intercourse with a syphilitic girl in succession the same night. All went through the primary and sec-

ondary stages and later on one developed tabes, and the other two paresis.

In spite of these potent arguments, there are many syphilologists who dispute the notion of a special toxicity. Chief among these is Heubner who asks: Why do some members of the same group remain free from involvement? Also how can nervous syphilis be considered a separate condition when in the same cadaver we find tabes or paresis along with gummous brain syphilis? He believes that gummata occur in the brain and cord just as they do in other parts of the body, and quotes cases from his own practice where one member of a married couple had nervous syphilis and the other visceral syphilis.

Ehrmann has made extensive investigations into the nerves of infected cases and has found a large number of treponemata in the nerves of the skin and subcutaneous tissue, especially where the prepuce was extensively ulcerated and excoriated. He found them embedded in the nerve fibers, surrounding the nerve bundles, in the lymph spaces, and in the connective tissue accompanying the nerve fasciculus. He believes that here may be found the explanation of tabes, especially when we consider that it almost always begins in the lowest part of the spinal cord.

Faulty treatment of the infection in its early stages is sometimes held to be a potent cause of nervous syphilis. (Fournier,[19] Kaposi, Neumann, Heubner,[20] Gilbert,[21] Kuh.[22]) Erb,[23] in 1900, called attention to the frequency of tabes in cases of an apparently mild infection, that is, in cases which were most apt to receive little or no treatment. Neisser[24] found that 57 per cent of all tabetic cases whereof he could find any record had received no antisyphilitic treatment. That an infection which was mild in its first two stages is more apt to result in brain syphilis is held by Broadbent, Fournier, Erb, and others. Theoretically this is all very well, but it has by no means been proved.

The question of extragenital infection has been brought up, but the consensus of opinion is that it does not appear to bear any special relation to brain syphilis (Nonne).

Although theoretically head trauma, by lessening the local resistance to any kind of infection should render the brains of luetics especially liable to involvement, as a matter of fact there

have been very few cases reported and it can probably be ruled out as a cause.

Intellectual strain or overactivity has been mentioned as a cause, but in 100 cases of cerebral lues Tarnowsky[25] only found six cases where this might have been assumed to exist.

Alcoholism is often found in cases of nervous syphilis and too much stress can hardly be laid upon the combination, syphilis and alcohol. Thus in Tarnowsky's 100 cases there were 45 who were habitual drunkards.

One other possible etiologic factor should be mentioned although it is now ignored. Neuropathic heredity is regarded by some (Oppenheim,[26] Fournier,[27] Lamy[28]) as having some influence in the causation of parasyphilitic diseases.

Nervous syphilis, according to Naunyn[29] and others, appears most frequently in the first years after the infection. Forty-eight per cent of all cases occur during the first three years and from then on the frequency decreases year by year. On the other hand, brain syphilis may appear very late. Nonne reports gummous processes in the brain after thirty years and Bruns[30] after forty years. Patrick[31] says that brain syphilis occurs most frequently during the first year, then the second, then the third, and after ten years it is exceptional. In general it may be said that brain lues can develop in any stage, but usually fairly late.

Two other factors may be mentioned, age and sex. There is a general impression that syphilis contracted late in life is apt to be severe and show nervous involvement, and men seem to be more often affected than women.

General Clinical Features.—When we come to consider the clinical features of syphilis of the nervous system we are dealing with an extremely indefinite, complex and kaleidoscopic picture. It is true of the nervous system that, to a degree unequaled by any other bodily system, it can present a great variety of disease pictures, each one of which may arise from a number of different causes. Likewise syphilis is well known to be able to simulate many different diseases. For example, a solitary gumma may exist in the brain for years without being recognized as such. Giving rise to headache, nausea, vomiting, insomnia and the like, it may be diagnosed as a brain tumor. Or the presence of epileptiform convulsions from the pressure of such a

gumma on a motor area may cause a diagnosis of epilepsy, indeed many such patients have been treated for years as epileptics. It is hardly surprising then that when we come to the combination of nervous syphilis we find a protean clinical picture. We must, therefore, bear in mind when looking for any disease entity or fancying we have recognized one, the possibility of syphilis as an etiologic agent. Otherwise we are likely to be misled by a close resemblance to some classical, neurologic type. This, of course, adds greatly to the complexity of the subject and emphasizes the need of minute inquiry into a possible syphilis, congenital or acquired, and the indispensability of all clinical and laboratory aids available.

At the present time the need which the profession has always felt for definite nomenclature is being satisfied, we believe, by the dividing lines drawn between congenital syphilis, acquired syphilis, and the parasyphilitic or metasyphilitic diseases. It may be that at some future time we shall regard tabes, paresis, cerebrospinal lues, etc., as variations of one and the same disease.

We shall understand the subject better then if we are not strictly bound to ideas of certain classical pictures, but rather think of a disease process, syphilis, which attacks the nervous system and, owing perhaps to a slight chemical or physiologic variation in the composition of the toxin or to a localized weakness of a certain part of the central nervous system attacks chiefly that part and thus produces a set of clinical symptoms which vary within wide limits.

Physiology of the Cerebrospinal Fluid.—Acquaintance with the physiology of the cerebrospinal fluid is desirable from the general standpoint that the normal must be understood to understand the abnormal, but, aside from this, what little is known of this particular subject should be clearly in the mind of the physician for at least two important reasons: in the first place, the dangers of lumbar puncture lie in the disturbance of the physiologic functions; in the second place, the rationale of intraspinous therapy is based on this physiology. These points will be taken up under lumbar puncture and intraspinous treatment, respectively.

The physiology of the cerebrospinal fluid is not well known, by any means. Entrenched as it is in life behind osseous fortifications, its study has been difficult and many theories have

been advanced by plausible investigators only to be disproved by later researches. A few known facts have crystallized out of the mass of speculation, however. The cerebrospinal fluid is obtained from three main sources; as a secretion from the choroid plexus, as a transudate into the subarachnoid and subdural cavities, and from the intraadventitial lymph spaces of the cortex. Not to go too deeply into its physical properties, it is uniformly alkaline, varying slightly if at all in this respect in widely differing psychoses (Weston).

It forms a sort of water-bed on which rests the base of the middle and posterior parts of the encephalon. It protects the brain from injury and the circle of Willis from compression and helps to dissipate the force of a blow. Its secretion and absorption are slow processes (A. and E. Cavazzani).[32]

Pathology.—The pathology of nervous syphilis is peculiar in that it was the starting-point for the study of this disease, but at present does not hold an equal position with the pathology of other nervous diseases. This is due largely to the fact that a comparatively efficient therapy has been devised for it, efficient to the extent that much fewer cases of nervous syphilis come to autopsy than of other organic nervous diseases.

In syphilitic disease of the bones of the cranium and the spinal vertebræ we find periostitis, ostitis and gummous formation. The characteristic lesions of the cranial bones, however, are exostoses and necroses occurring side by side. Although syphilis of the cranium is fairly common, this is not true of the vertebræ. When it does occur the cervical section is most apt to be affected, and the disease process, unlike tuberculosis, attacks the spinous and transverse processes.

Speaking generally of the pathology of nervous syphilis we may divide it into four manifestations: The syphilitic new growth, the chronic hyperplastic inflammation, disease of the blood vessels and primary parenchymatous degeneration.

Syphilitic new growths, or gummata, may be small or large, simple or multiple. They may vary in size from a pinhead to an orange, the favorite size being about that of a walnut. The favorite location is the dura, either of the convexity or the base. They have been found in the brain in the frontal, parietal, temporal, and occipital lobes, in the fourth ventricle and the cere-

bellum, pons, medulla, and hypophysis. On cutting open a typical gumma of the brain we find in the center a yellow, necrotic mass in which the cells can not be distinguished except for occasional giant and epithelioid ones; this central area is surrounded by a grayish, translucent tissue and the whole encapsulated with a reddish or brownish substance which is hard in proportion to its age. In the outer layers of the gumma are found granulation tissue composed of spindle and star-shaped cells. The blood vessels are almost entirely destroyed except in the periphery where they appear diseased. From the gumma, disease processes extend directly into the brain, including the meninges. The epicerebral space disappears, the Meynert layers of cells become indistinguishable by displacement or disease and round cells cover the blood vessels. The nerve tissue itself is profoundly diseased. Round cell nuclei are found and new capillaries appear. The ganglion cells undergo significant changes: they shrink, lose their thin layer of protoplasm in which the Nissl bodies are indistinguishable—finally the nuclei themselves become absorbed.

Syphilitic meningitis may be gummous or of the fibrous, hyperplastic form, usually a combination of the two. The leptomeninges form usually the starting point and the disease process frequently extends to include all three membranes. A simple meningitis may occur as may also a localized one, but both conditions are rare. Usually the base and convexity are affected also. In basilar meningitis extensive injury occurs to the brain tissue at the base, including the large arteries and the cranial nerves.

A most important part of the pathology of nervous syphilis is disease of the blood vessels. They may be mechanically compressed, resulting in occlusion of the lumina, or thrombi may occur, or the walls may become thickened giving the same result. Sternberg and Lancereaux are responsible for the now generally held opinion that the most important clinical symptoms are those resulting, directly or indirectly, from disease of the blood vessels. The beginning of the entire process seems to be an inflammatory process in the perivascular lymphatics, as is the case in other lesions. The end result is inevitably the obliteration of the lumen of the vessel. This obliterative endarteritis (first described by

Heubner)[33] was demonstrated by Cornil and Ranvier in 1872 to be the same kind which occurs after the application of a ligature, although it is true that luetic individuals are particularly predisposed to it. Köster[34] holds that this intimal thickening is secondary to areas in the media which have developed from the vasa vasorum, and it is for this reason that endarteritis is

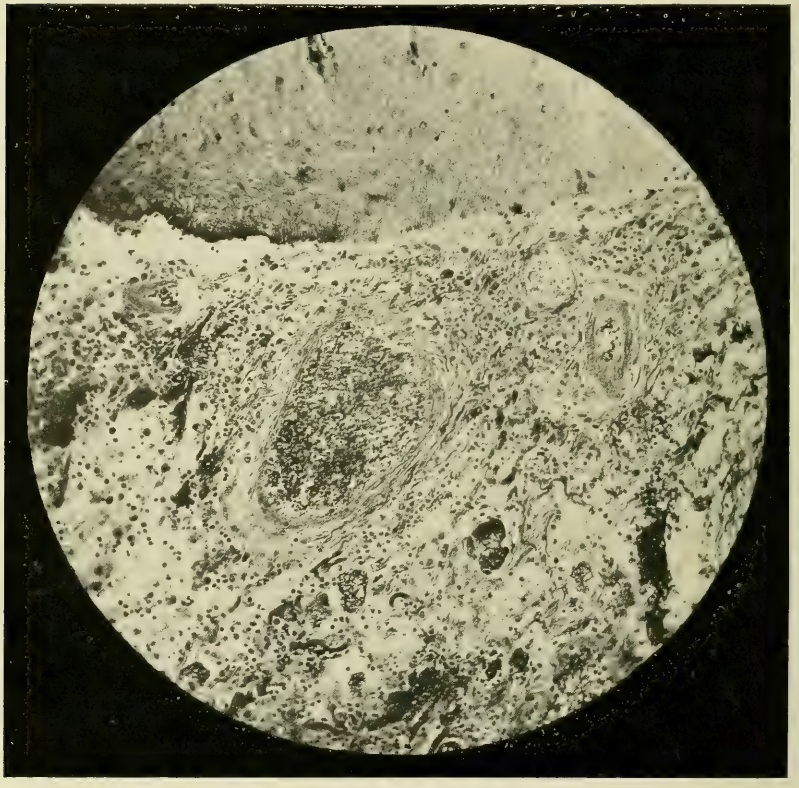

Fig. 122.—Late syphilitic meningitis shows the same changes as other syphilitic lesions. (Collection of Drs. Fordyce and MacKee.)

so common in the brain where even the small arteries have the vasa vasorum.

The final result of the shutting off of the circulation of definite areas of the brain is a profound disturbance of nutrition, sometimes resulting in absolute necrosis of the parts supplied. Ruptures and secondary hemorrhages sometimes occur.

Diagnosis.—The diagnosis of syphilitic disease of the central nervous system presents the encouraging picture of a subject emerging from considerable complexity and obscurity into a region of comparative clearness. At every turn new diagnostic refinements, chiefly at the laboratory level, are being perfected.

If the practitioner will be on the *qui vive* in two directions, there is but small chance of his missing the diagnosis of early syphilis of the nervous system. First, in all syphilitic patients he should bear in mind the possibility of involvement of the central nervous system and be ever watchful for neurologic or clinical symptoms indicating such involvement; and, second, he should remember, in every case showing neurologic symptoms, the prevalence of syphilis and attempt to rule it out as an etiologic factor, first of all.

In carrying out the first half of this program the physician should tabulate all the cases of syphilis in his practice *and examine them at regular intervals during their life time.* Just how early the spinal fluid may become affected is a point bearing on which we have all too little evidence. We know, however, that a pleocytosis may appear in the fluid very early in the course of the disease; Ravaut has found it two months after infection. In cerebral syphilis, tabes, and paresis, the first symptom to appear may be this pleocytosis; it may occur as long as two years before any neurologic symptoms are demonstrable. These patients should be impressed so forcibly with the idea that this examination is indispensable to their welfare that they submit themselves to it regularly and voluntarily. This routine investigation should include a review of the patient's activities since the last examination (to detect a possibly incipient general paresis), a testing of the chief reflexes, special attention being given to the pupillary reflexes, a Wassermann reaction with the blood serum and a complete examination of the cerebrospinal fluid. Such a routine examination, including the fluid examination, should be made once a year, and if possible, the same examination, exclusive of the fluid, every six months.

The clinical findings, speaking generally, which should give rise to suspicion of central nervous system syphilis may be divided into three parts,—disturbances of the reflexes, tremors, and disturbances of coordination. In examining the reflexes, by

far the most significant are the pupillary ones, but several of the more important and easily elicited deep and superficial ones should be tested. The chief deep reflexes to be examined are the patellar, the tendo Achillis, the triceps, the biceps, and the jaw. Many others may be examined if desired, but a careful test of these five is usually sufficient for the purpose indicated. The idea is to place a muscle in a state of partial tension, divert the patient's attention from it, and give a sharp tap on the tendon. A normal response is a quick contraction of the muscle; only with experience can come the feeling that the reflex is normal,—beginners are apt to call it exaggerated. The patellar, or knee reflex, is the simplest and most easily elicited of all. The patient sits with crossed knees, his attention is directed to the ceiling, and the tendon is tapped just below the knee cap. In testing the tendo Achillis the patient kneels on a chair with his face to its back and his feet projecting forward over the edge of the seat. The tendon just above the heel is tapped. In testing the triceps the patient flexes his forearm slightly and the tendon of the triceps is tapped just above the olecranon process. The biceps is tested for by having the forearm semiflexed on the arm, the physician places his finger over the biceps tendon and taps the finger. In testing the jaw reflex the patient opens his mouth a little, relaxing the muscles of mastication. The examiner places his finger on the lower jaw between the lip and chin and taps it; a positive result is a sudden closure of the jaw.

Many superficial reflexes may likewise be examined, but in the routine examination advised above where the physician is searching for a possible beginning disease of the central nervous system, three probably are sufficient, the plantar, the corneal, and the pharyngeal. In testing for the plantar reflex the sole of the foot is stroked with a hard object such as the handle of an instrument, giving a flexion of the toes. While examining for this reflex the physician should not neglect to search for the Babinski, which is its antithesis. The Babinski reflex is obtained when the outer side of the sole of the foot is stroked firmly from the heel to the toe; it is an extension of the great toe and, often, a separation of the other toes. The presence of this reflex is of great importance as it practically always indicates a disease process in the corticospinal motor pathways. The cor-

neal reflex is tested for by touching the cornea lightly, which causes a quick contraction of the sphincter palpebra; touching the base of the tongue or the pharynx gives the phenomenon of "gagging."

The neurologic examination of the eye reflexes is the most important of all and should be carried out with scrupulous care. Uneven or irregular pupils, disturbances of light, accommodation, of consensual reflexes and most significant of all the Argyll Robertson pupil, are all indicative of disease. The Argyll Robertson syndrome, when present on both sides, and permanent, is said by some authorities to be *proof* of syphilis of the central nervous system. The weight of the leading authorities seems to be that, while this diagnostic sign may occur in very rare instances without syphilis, it "is nearly enough positive for syphilis to permit one to assume its presence, and to therapeutically guide one's self accordingly." (Rose.)[35] It might be mentioned here that fixed pupils may occur in chronic alcoholics, but they become motile after a time when alcohol is withdrawn.

The fully developed Argyll Robertson syndrome consists in loss of reaction of the pupil to light while it reacts to accommodation. The simplest way to test this is to have the patient face a window and look through it at a distant object. This, of course, causes the pupil to dilate; then the reaction to light is tested by the physician covering and uncovering the patient's eyes with his hand. Instead of this a sudden access of light can be introduced into the eye by a pocket flashlight, but it must be remembered that the stimulus of a sudden and comparatively brilliant light of this kind may paralyze temporarily the nervous mechanism so that the pupil does not contract. Elaborate apparatus have been devised to test the light reaction, but they are too complicated and expensive for the average practitioner. The happy medium seems to be for the physician to make repeated examinations, in the daylight and in the dark room, and if practicable, check up his observations by an examination by an ophthalmologist. After all, "pathologic alterations in the pupillary reflexes are only chance happenings * * * It may be possible for a syphilitic process to permanently destroy portions of the pupillary reflex paths, and be completely and permanently arrested. The pupillary reflexes, however, remain impaired.

* * * A pupillary anomaly may exist as long as from twelve to sixteen years (alone) and then the patient may develop a paresis or tabes." (Jelliffe and White.)[36]

The laboratory or serologic diagnosis of central nervous syphilis has been making such tremendous strides in recent years that by means of certain tests, combined with the neurologic findings, an almost certain diagnosis of congenital or acquired syphilis, or of the so-called para- or meta-syphilitic diseases can be made. Great stress has been laid on the "four reactions;" the Wassermann in the blood, the Wassermann in the spinal fluid, the protein content of the spinal fluid, and the cell count in the spinal fluid. Theoretically the percentage of positive Wassermanns in the blood in the early stages of nervous syphilis is 100, in practice this percentage may sink to 75 or even to 50. There are several reasons for this—active treatment, alcohol, etc. It may be mentioned also that the Wassermann reaction in the blood has also been found in leprosy, yaws, malaria, and scarlatina, but the exclusion of these is seldom difficult. After all it "can no longer be regarded as specific; but only as characteristic of syphilis." (Nonne.)[37]

The examination of the cerebrospinal fluid is the most important part of the laboratory diagnosis and, when done by an expert, it is quite usual to be able to establish the diagnosis beyond question by this method alone. Lumbar puncture should be insisted upon to the patient and his relatives wherever there is the slightest suspicion of central nervous system involvement. Under proper precautions the danger is infinitesimal, but there is a slight element of risk, and sudden death has followed the withdrawal of fluid from patients who have brain tumor or high blood pressure so that if these conditions be suspected the greatest care must be exercised. Von Schneider reports a case of precox who had one episode precipitated by alcohol, with apparently complete recovery, and who had a second and permanent upset, apparently caused by a lumbar puncture. Neurotic individuals are apt to react badly and to complain of headache, nausea, vertigo, and lumbar pains for days or weeks afterwards. The same symptoms often occur in fairly normal individuals for a day or so after the procedure. It must be remembered that the cerebrospinal fluid has functions of which we

are in ignorance, but it is generally believed that it has something to do with the maintenance of pressure and when we withdraw a quantity of fluid we may seriously disturb the intracerebral equilibrium with grave results. In describing the technic of a lumbar puncture it is customary to say that either the sitting or the recumbent posture may be used, but as a matter of fact the weight of authority is overwhelmingly in favor of the lateral recumbent position. Practically all the German and French authors favor it, and the only authority of any consequence in this country who favors the sitting posture is S. R. Miller,[38] of Johns Hopkins Hospital. The latter position carries with it the danger of cerebral vascular disturbances or hernia of the medulla into the foramen magnum. Hough* says that there is frequently a difference of 200 mm. of water pressure between the two positions, and that bad after-effects are much more common when the sitting posture is used. Quincke, quoted by Oppenheim, recommends the left lateral position, well bent forwards at the lumbar portion of the vertebral column. The better the surgical technic observed, the less danger there will be from such an accident as infection. Remember that it *is* a surgical procedure, during which a cavity containing a very delicate and important structure is entered with a sharp instrument.

Draw an imaginary line uniting the highest parts of the iliac crests; this will generally pass over the fourth lumbar spine. The needle is introduced on or below this line. The best needle is a long, slightly flexible, very sharp one, at least 12 cm. long and having a well fitting stilet. The skin having been sterilized, the operator palpates the spine with the tip of his fingers until he feels that he knows exactly the position of the spines of the vertebræ. A spray of ethyl chloride may be directed on the site of puncture, but is usually not necessary. The needle is introduced about 1 cm. to the side of the median line and directed inward and slightly upward. It passes through the skin, subcutaneous tissue, spinal muscles, ligamentum flavum, dura, and arachnoid. If the puncture is made in the middle line, as may be done in the case of children, the interspinous ligament is also pierced. At a depth ordinarily

*Private communication.

of 4 to 6 cm., but in muscular or fat individuals of 8 to 10 cm., the resistance to the needle suddenly ceases and the operator "feels" that he is in the subarachnoid space. The stilet is then withdrawn and the fluid escapes, usually drop by drop, but sometimes with a spurt, and is collected in a sterile tube.

If the operation has been properly performed, a "dry puncture" is a *rara avis* and is usually due to obstruction of the needle or failure to perforate the dura. Occasionally the patient will complain of severe pain in one leg; this is due to contact of the needle with a caudal root, disappears very quickly, and is not important. The minimum amount of fluid necessary for the contemplated tests should be withdrawn and the patient kept in bed for twenty-four hours. Care should be exercised that the patient does not suddenly straighten out his back while the operation is in progress as this may break the needle.

The pressure of the cerebrospinal fluid may be estimated if desired by apparatus especially designed for this purpose, but in the case of nervous syphilis it has no diagnostic value. (Nonne.)

The Wassermann reaction in the spinal fluid (first demonstrated by Plaut and Wassermann) is nearly always positive in general paresis, but rare in tabes and cerebrospinal lues unless large quantities of the fluid are used. Nonne, in his second edition (1916) has summed up the "four reactions" admirably as follows:

General Paresis or Taboparesis.—

1. Wassermann reaction in the blood positive (nearly 100 per cent).
2. Phase I, (Nonne and Apelt's [39] method of estimating an increase of globulin by ammonium sulphate), reaction positive—(95 to 100 per cent).
3. Lymphocytosis marked (95 per cent).
4. Wassermann reaction in the fluid positive (using 2 c.c., 90 per cent; using larger quantities 100 per cent).

Tabes (without combination with paresis).—

1. Wassermann reaction with blood serum positive (70 per cent).
2. Phase I, reaction positive (95 per cent); usually strong.
3. Pleocytosis (90 to 95 per cent) usually strong.
4. Wassermann reaction in the spinal fluid (using, 2 c.c., positive in about 20 per cent; larger quantities almost 100 per cent).

Cerebrospinal Lues.—

1. Wassermann reaction in blood serum positive (70 to 80 per cent).

2. Phase I, reaction usually positive, but not so strong as in paresis or tabes; exceptionally negative.

3. Pleocytosis, almost always positive, but not so marked as in paresis and tabes.

4. Wassermann reaction in spinal fluid (using 2 c.c., positive in about 20 per cent; large quantities of fluid almost always positive).

The above table can be taken as a convenient diagnostic one for the general practitioner to use, but a little more detail about the diagnostic criteria involved may serve to make the subject somewhat clearer. The Wassermann in the blood serum has already been discussed. The Wassermann in the spinal fluid is a very important diagnostic method inasmuch as it is nearly always positive in syphilis of the nervous system and nearly always negative in syphilis without nervous involvement.

Using the usual quantity of fluid (2 c.c.), it may be said for all practical purposes to be positive in every case of general paresis, in one out of five cases of tabes and cerebrospinal lues, and negative in multiple sclerosis, cerebral and spinal tumors, etc.

The increase of lymphocytes in the fluid, or pleocytosis, is not so significant as the Wassermann, but it is important. Pleocytosis occurs in about 95 per cent of syphilitic and metasyphilitic affections of the nervous system. In organic, nonsyphilitic nervous diseases it may occur, but seldom with such intensity. It must be remembered, however, that sometimes there is no lymphocytosis in old cases of tabes. Also, as pointed out by Merzbacher, about one-third of all syphilitics may sometimes show a moderate lymphocytosis without any clinical symptoms of organic nervous disease. Alzheimer has devised a technic which enables us to make a differential count of these cells and there have been many attempts to settle upon a pathognomonic cell-picture for paresis, for example. Thus the "mast cell" at one time was fixed upon as the *sine qua non* of paresis, but no one believes this today. The Fuchs-Rosenthal method is probably the most convenient for counting the cells; it makes use of a counting-chamber similar in principle to the leucocyte counting apparatus but somewhat larger. The counting is performed as follows (Nonne): The staining fluid (0.1 gm. ethyl violet, 2 gm. glacial acetic, 50 gm. distilled water) is drawn up by

the pipette, in general use for white blood cells, to point I, and then further filled with the liquor to point XI. After shaking the pipette for five minutes, a drop of the mixture is put on the counting chamber. All lymphocytes and leucocytes in all the squares are counted and the total divided by three. Five cells or under per cubic millimeter is considered normal, six to ten doubtful, and more than ten pathologic.

More complete and satisfactory than the Fuchs-Rosenthal[40] counting chamber method, is the Alzheimer[41] method which in fact is the most complete and satisfactory of all. By this method the cells may be counted and differentiated with great accuracy; it is, however, not so rapid as the Fuchs-Rosenthal chamber which is more popular in large hospitals and other places where a great deal of laboratory work must be done in a short time.

An increase of the protein, or globulin content is considered pathologic and the simplest method of estimating this is by the method of Nonne and Apelt—the so-called "Phase I." One c.c. of spinal fluid is added to the same amount of a hot saturated solution of ammonium sulphate which has been allowed to cool. One of these liquids is poured gently on top of the other and if there is an increase of the globulin content a gray ring appears at the line of contact. Then the liquids are shaken together and observed after three minutes. If the resulting mixture is cloudy, the reaction is positive.

A comparatively new test which has obtained great popularity in the last few years is the goldsol reaction, commonly referred to as the "Lange colloidal gold curve." The principle of this reaction depends upon the precipitation of gold out of a colloidal gold solution caused by the changing ratio of protein content. It is useless to attempt to perform this test unless one is an expert laboratory technician, but a brief description of it may be of theoretic interest: Ten tubes, which have been cleansed meticulously, are partly filled, nine of them with one c.c. of normal salt solution and 0.2 c.c. of the fluid to be examined. The first tube is shaken well and one c.c. of its contents removed and placed in the second tube which is then shaken and one c.c. of its contents transferred to the third tube. This process is continued down the line and the one c.c. obtained from the tenth tube is thrown away. Next the goldsol solution

is used; this must be port-wine red in color, perfectly transparent and free from any tinge of purple. The colloidal gold solution is made up from the following ingredients:

a. Doubly distilled water b. Gold chloride crystals (yellow) c. Potassium carbonate d. Formalin	Merck's "Blue Label" Reagents.

One liter of water is heated to 60° C. in a sterile Jena beaker. At this temperature 10 c.c. each of a 1 per cent solution of gold chloride and a 2 per cent aqueous solution of potassium carbonate are added synchronously and thoroughly mixed at once. From this point the solution is heated as rapidly as possible, by using a four or six flame bunsen burner, until a temperature of about 90° C., but not exceeding 95° C., is reached. The flame is turned out, and while the contents of the beaker are briskly agitated, 10 c.c. of 1 per cent aqueous solution of formalin are gradually added. The previously clear, colorless liquid at once undergoes a brilliant reaction, with reduction of the gold to a colloidal state, shown by the production of a beautiful play of colors. (S. R. Miller.)[42] Five c.c. of this solution are added to each tube which is then well shaken. Within a few minutes a change in the color of the tubes may be noticed, but the final reading should not be made for at least 12 hours. The result is expressed graphically by numbers; a complete reduction, where the fluid in the tube resembles water is called 5; bluish water, 4; blue, 3; violet, 2; bluish red, 1; and the unchanged, or port-wine red, 0. The result is then expressed by ten figures in a row, each representing a tube. In general paresis the first few tubes show complete or nearly complete reduction, the next few partial reductions and the reaction tapers down to none at all in the last few tubes. Thus a typical paretic curve would be something like this: 5554432100. A typical cerebrospinal lues curve would be 1133210000. In nonspecific meningitis, as tuberculous, in the comparatively few cases reported, the greatest color changes have occurred in the 5th and 7th tubes (Nonne).

The opinions regarding this test are divided. Some think that a typical paretic curve means paresis beyond question, but

J. E. Moore of Johns Hopkins has found this result in cases of multiple sclerosis.

S. R. Miller, after a careful study of this reaction in 171 cases, came to the following conclusions: 1. The colloidal gold test is essentially a laboratory method. It can be performed rapidly and with a minimal amount of spinal fluid. 2. Extreme care in the preparation of reagents and the cleaning of glassware is imperative. 3. Normal fluids give negative reactions. 4. The test is of no aid in the diagnosis of purulent or tuberculous meningitis. 5. It has no known advantage over known laboratory procedures in the diagnosis of congenital syphilis. 6. Reactions in secondary and tertiary syphilis are inconsequent. Their significance when present is not known. The statement that they indicate the earliest stages of central nervous system involvement lacks proof. 7. The positive reactions observed in the majority of cases of tabes and cerebrospinal syphilis are not characteristic. 8. We feel that the reaction peculiar to paresis is sufficiently constant to warrant its use as an aid in the differentiation of this condition from others with which it might be confused. 9. It is possible that the test may prove to be more sensitive than those at present employed, as an indicator of the results of specific therapy in syphilitic diseases of the central nervous system. 10. Much may be expected from the application of colloidal chemistry to the study of biological problems.

There are a few other tests which might also be mentioned, although with those given above the practitioner may be said to be fairly well equipped. Thus there is the phosphoric acid test which was thought by Donath to be significant as indicative of the decomposition of lecithin. Its value is doubtful, however. The same may be said of the hemolysin reaction (Von Weil[43] and Kafka).

In conclusion it must be borne in mind that the use of all four reactions is not conclusive in all cases, as anomalous results have been reported. The blood serum has been found negative in general paresis and all four reactions have been found negative in tabes, especially in long-standing cases. Careful clinical and neurologic examinations are indispensable accompaniments to the laboratory test.

Prognosis.—The prognosis of syphilis of the central nervous system is difficult to discuss generally, depending, as it does, so greatly on the stage of the process, the part of the nervous system attacked, and the intensity and persistence of the treatment. As a general statement, it may be said that there are only a limited number of cases, and these usually the early ones, where we may expect complete recovery. Nonne thinks that physicians, as a rule, are much too optimistic in their prognosis of syphilis of the central nervous system. Only where all four reactions become negative may we speak of cure and then only at the laboratory level; this must be combined with recovery at the physical and psychologic levels.

The prognosis of the various clinical forms of nervous syphilis will be discussed below; we can only say here that the prognosis is as a rule bad, even hopeless—or practically so—in such diseases as paresis; that where the process has extended so as to destroy nervous tissues the actual damage done may be said to be irreparable; but, on the other hand, in many cases, arrest or even cure may be obtained by early and intensive treatment, especially by the newer methods, discussed below.

Prophylaxis.—The avoidance of specific infection is, after all, the treatment, *par excellence*. The danger of illicit sexual indulgence should be ever present to the patients of the general practitioner. This does not apply, of course, to extragenital infection. The problem of the national control of venereal disease is a large one, and can not be discussed here, but possibly in it will be found the solution of the syphilis problem.

Remembering that patients of neurotic make-up are especially liable to the encroachment of syphilis on the central nervous system (Oppenheim) such patients should be kept under careful watch, and all patients known to be syphilitic should be warned, solemnly and repeatedly, against excesses in alcohol and venery. Wherever practicable, such patients should also avoid mental overwork, or severe emotional strain.

Although there is some difference of opinion as to the effect which energetic treatment of the primary and secondary stages of syphilis has on the occurrence of central nervous syphilis, the preponderance of evidence seems to point to a thorough and intelligent treatment of the disease in its early stages as a pre-

ventive. This treatment does not differ when intended to prevent nervous involvement from that given ordinarily and will be found discussed elsewhere. Furthermore, many luetics become hypochondriac and it has been observed that years of apprehension that they would develop tabes or paresis have in many cases actually been followed by one or the other of these diseases: whether or not these cases can be classed as coincidences or not has not been settled, the fact remains that syphilophobia is not a healthy state and should be combated with all the psychotherapy in the physician's armamentarium.

The importance of being on the *qui vive* for the first appearance of nervous syphilis must be reiterated. When we consider that in some cases the only hope of recovery lies in early diagnosis and that in other cases, such as paresis, failure to recognize the disease early may cause the patient and his family untold suffering, the importance of constantly regarding every luetic as a potential paretic can hardly be overestimated.

The subject of prophylaxis should not be left without quoting a treatment advocated by two prominent syphilologists, Neisser, of Germany, and Fournier,[44] of France, for the prevention of paresis. Fournier recommends giving vigorous mercurial treatment for two years after the beginning of syphilis, then stopping all treatment for two years, then giving another year of treatment, a year or two of intermission, and then another year of treatment. This has been called the chronic intermittent treatment and, in spite of its illustrious exponents—and it has also been indorsed by such men as Gowers and Perl—is not favored by the vast majority of opinion.

Treatment.—The treatment of syphilis of the central nervous system may be divided, looking at it one way, into therapeutic agents introduced directly into the central nervous system and those reaching it indirectly and, from another viewpoint, into arsphenamine and mercury and iodides. The general plan, however, is the pursuance of a general antisyphilitic attack, modified to meet the physical and physiologic peculiarities of the central nervous system. On account of the extreme importance of the central nervous system and the extensive damage which physically minute lesions can bring about, nothing less

than a complete sterilization of the tissues should be our aim, and this is difficult of attainment.

It seems to be generally agreed that, whatever other therapy is used, some form of mercury should be given in conjunction with it. Mercury inunction has its ardent advocates, Erb and others claiming that it is particularly suited to nervous syphilis, combined with iodides. Neumann, of Vienna, believes that inunctions are quicker and more thorough in their effect than any other mercury methods. These may be supplemented by intramuscular injections of mercury.

The general opinion, culled from the literature, is that mercury is effective in all stages of syphilis and iodine in the later ones, although iodine may influence favorably some symptoms which occur in the early stages, such as occipital headache. Iodine, moreover, is thought to act most efficiently on gummous lesions.

The surgical interference with specific brain tumors has been a mooted question, its chief advocates having been Horsley[45] and Gowers. In 1898 Schlesinger and Friedländer formulated the following conclusions, which still hold good: Surgical interference is justified in the case of a syphilitic brain tumor which progresses in spite of treatment, if an *indicatio vitalis* exists, or if Jacksonian epilepsy appears, or if the tumor, after antispecific treatment, is small and easily accessible. The addition of arsphenamine and neoarsphenamine to the armamentarium of the neurologist has greatly increased his power of attack. The ordinary intravenous method of administering them need not be discussed here, except to say that in some cases of nervous syphilis a combination of the intravenous administration of arsphenamine with the free use of mercury seems to be a sufficient therapeutic attack.

The fact that in some cases arsphenamine exercises a definitely harmful effect on the nervous system should not be ignored. This is especially true where there is a disease of the optic nerve and Finger[46] has called our attention to the increase of incidence of disease of the acoustic and facial nerves since arsphenamine has been so generally used. There have also been deaths (from encephalitis and meningomyelitis) attributed to it.

Leaving out of the question the undoubtedly favorable in-

fluence of arsphenamine on ordinary syphilis, the fact remains that when the treponemata have once ensconced themselves in the nervous system they are not easily reached. In fact, "careful chemical investigation of the cerebrospinal fluid has heretofore failed to obtain any trace of arsenic when arsphenamine has been given in the usual manner." (Jelliffe and White). Just why the arsenical compound should not reach the spinal fluid or, at least, why it reached it, if at all, in such minute quantities or in such a chemical combination that it is neither demonstrable by the usual test nor does it influence the spinal symptoms at all is not fully understood as yet. It is believed that the chief source of the cerebrospinal fluid is by way of the choroid plexus and here a filtration process takes place. It may well be that the organic compound of arsenic circulating in the blood after an injection of arsphenamine is caught in this filter and does not pass on to the intraspinal canal. This led, by an obvious logical process, to the idea of placing a spirocheticidal agent directly in the spinal canal. This method, which was experimented with by Swift and Ellis, was soon found to be extremely dangerous, and so dropped.

Next came the idea of injecting the serum of patients who had already received arsphenamine medication directly into spinal canal. Intrathecal medication of this sort appears to have been first done by Marincesco, in 1911, for disease of the spinal cord. In 1913 Robertson experimented with it in paresis. But the Swift-Ellis method, based upon the experiments of Swift and Gander, seems at present to be the most promising of all. It is as follows: one hour, after an intravenous injection of arsphenamine of from 0.3 to 0.5 gm., 40 c.c. of blood is drawn directly into a sterile centrifuge tube and, after the clot has formed, centrifuged. The clear serum is then pipetted off into a sterile glass container, firmly stoppered with sterile cotton, and set upon the ice until the next day. It is then heated in a water-bath at a temperature of 56° C. for half an hour. Twelve cubic centimeters of the serum is diluted with 18 c.c. of normal salt solution, making a 40 per cent solution, and introduced into the lumbar part of the spinal canal. At subsequent injections the amount of the serum may be gradually increased and the salt solution decreased, using 15 and 18 c.c. of serum and 15 and 12

c.c. of salt solution, respectively. The undiluted serum is also given without causing symptoms of irritation.

Before introducing this salvarsanized serum into the spinal canal, more than 30 c.c. of spinal fluid should be withdrawn, so that there will not be an increase of cerebral pressure, which might be very injurious. Just why this method should give such good results is not known, for the actual amount of arsphenamine in the serum injected must be extremely minute. We can only account for it by supposing that an agent of some kind is generated in the patient's blood serum, during the few hours following the intravenous injection of arsphenamine which has powerful spirocheticidal action, but what the agent is we have no notion.

Mention must also be made of the method by which Ravaut[48] has obtained good results, that is, combining the intraspinal injection of neoarsphenamine in 3 to 6 mg. doses with the intravenous injection of arsphenamine. Also Fordyce,[49] in the Vanderbilt clinic, has been adding a small amount of arsphenamine to the salvarsanized serum before it is injected intrathecally and reports favorably on this method.

Another intrathecal treatment of nervous syphilis which promises well is that by mercurized serum, originated by Byrnes[50] of Johns Hopkins Hospital. Byrnes, after experimenting with the direct introduction of mercury into the spinal canal and finding it dangerous, evolved the following technic:

From $\frac{1}{50}$ to $\frac{1}{30}$ grains of bichloride of mercury is dissolved in 5 c.c. of freshly-made sterile normal salt solution. This is added to 20 c.c. of serum obtained from centrifuged blood withdrawn from a vein. This solution of serum and mercury is then heated in a water-bath at 56° C. for one-half hour, so that an albuminate of mercury is formed which is then injected into the spinal canal at body temperature. These injections are repeated at intervals of from two to three weeks, depending upon the progress of the case.

Other methods of intrathecal therapy must be mentioned at least for each has its advocates and its remarkable results. Thus Sicard and Reilly, under local anesthesia, trephined the skull and injected neosalvarsan under the arachnoidea cerebralis. Levaditi, Marie, and Martel trephined paretics over

the frontal bone and administered the salvarsanized serum between the dura and the frontal lobes of the brain. Since then Marincesco has injected salvarsanized serum *in vitro* both intraspinally and intracerebrally in cases of tabes and paresis. He gave from 6 to 12 mg. of arsphenamine in this way every week. Gennerich recommends endolumbal treatment; he injects every three weeks from six to eight c.c. of a solution of 0.15 neosalvarsan dissolved in 300 c.c. of normal salt solution, mixed with equal parts of spinal fluid. Cimbal recommends dissolving the neoarsphenamine in the spinal fluid. He gives doses of not more than 3 mg. of neosalvarsan in this way. Nonne considers this last as the best method of giving arsphenamine intraspinally we have today.

The tuberculin treatment of Wagner von Jauregg is based upon the ancient observation that infections, particularly those accompanied by the formation of pus, have a favorable effect on psychoses; this led to experiments with paretics of the injection of tuberculin. Von Wagner claims that cases thus treated usually improve and often have a remission sufficiently complete for them to resume their occupations. Cases where there is no suspicion of tuberculosis receive an initial dose of 0.01 of Koch's old tuberculin; if tuberculosis is suspected 0.001 is given. The dosage is increased gradually, 8 to 15 injections being given.

Donath uses sodium nucleinate to produce an artificial infection; 2.5 gm. of this is dissolved in 100 c.c. of normal salt solution and 40 c.c. injected intramuscularly. Five days later 60 c.c. are given, then 80, then 100. At this point 0.5 gm. more of sodium nucleinate is added to the solution each time until 4 to 5 gm. are given at each injection. Plaut[51] uses this treatment in conjunction with salvarsan therapy. Dölken gets his leucocytosis by the use of various vaccines.

A word of warning may be said here about pursuing therapy too far. Sometimes the clinical aspect of the case is not sufficiently regarded, but medication is pushed in an effort to make the spinal fluid absolutely negative. Also where the spinal fluid findings remain negative, or nearly so, but there are marked clinical or neurologic symptoms, or both, the intravenous method is the method of choice, rather than the intrathecal.

On the other hand, in spite of all reasoning to the contrary or lack of clear understanding of the rationale, it is undoubtedly true, and a commonplace in the practice of every neurologist, that there occur cases in which intensive treatment of other kinds has no effect whatever, but which clear up remarkably under intraspinous therapy. Nonne, undoubtedly one of the greatest authorities on the whole subject, in his latest (1916) book, has this to say, after recounting all the methods of therapy, direct and indirect, intravenous and intraspinous. "Whether the endolumbal treatment of syphilogenetic disease of the nervous system, be it by the direct method of Ravaut, Gennerich and Cimbal, or the indirect one of Marincesco, Swift and Ellis, is more effective than the intravenous is as yet not determined. Communications of Eskuchen, Weygandt, Cimbal, and V. Schubert, as well as my own experiences, are not convincing. A longer period of observation will be required before definite conclusions can be formed."

We may say, generally speaking, that intraspinous therapy, after the manner of Swift and Ellis, should at least be tried in the early stages of such diseases as cerebrospinal syphilis and paresis. In well advanced cases of paresis it is useless to submit the patient to such a troublesome and expensive treatment. In early cases of nervous syphilis, where the blood becomes negative to the Wassermann reaction and yet the spinal fluid continues to show positive signs, theoretically intraspinous therapy is clearly indicated, and indeed in practice it often gives good results.

There are cases of tabes which may remain stationary and benign for years, even with marked pathologic findings in the spinal fluid, and such cases are best let alone. Also some cases of paresis go to pieces and die very quickly when treated vigorously. The beneficent therapeutist, then, proceeds cautiously with this antisyphilitic therapy, feeling his way along with one eye on the spinal fluid and the other on the patient himself and does not let his *furor therapeuticus* blind him to the welfare of the patient.

Syphilis of the Cranial Bones and the Vertebræ

The symptoms arising from syphilis of the cranium are quite commonly headache and, if the lesions are large enough to cause

pressure, the usual symptoms of tumor of the brain; in the vertebræ symptoms arise when, as a result of hyperostitis or gummous formations, there is pressure on the cord. Circumscribed gummata of the cranium, pressing into the cerebral lobe, are not frequent. In about one-half of the cases of osseous syphilis, the cranium is affected. The frontal bone is most frequently affected, with the parietal next. It must be borne in mind, however, that, surprisingly often, extensive syphilitic disease of the cranium may occur, with no involvement of the brain. Much rarer is syphilis of the vertebræ; it usually attacks the cervical part of the column.

Cranial bone gummata may exist for years, giving rise to no symptoms other than epileptiform convulsions. Such cases often go on to autopsy diagnosed as epilepsy. Other cases show symptoms of brain tumor, headache, vertigo, projectile vomiting, and insomnia.

Syphilitic Basilar Meningitis

This is a quite common condition, as *syphilis of the nervous system shows a predilection for the base of the brain.* Rumpf[52] explains this by anatomic reasons: The rich supply of blood and lymph vessels to this spot affords a favorable breeding place for the microorganisms. Furthermore the arachnoid in the regions of the sella turcica, the optic chiasm, and the lamina perforata anterior, offers inviting gaps for germ invasions.

The symptoms of syphilis of the meninges at the base are characterized, as is so frequently the case in organic disease of the brain, by multiplicity, transiency and vagueness. Quite commonly the brain tissue itself is involved, complicating the picture. The symptoms of meningitis of the convexity and of the base vary somewhat, but a combination of both forms exists very frequently.

The Wassermann reaction with the blood serum is positive in a slight majority of the cases, in the spinal fluid it is usually negative with 0.2 c.c., but becomes positive when large amounts are used; very rarely it remains negative. The Nonne-Apelt, Phase I, is nearly always positive, usually strongly so. There is usually pleocytosis, the lymphocytes being somewhat increased.

Headache is a frequent symptom, sometimes becoming more

intense at night. The patient will often complain of pain "deep in the eyes." Percussion over the frontal region may elicit tenderness. Vomiting and vertigo are common. Optic neuritis and choked discs are more usual in the basilar than in the other types. There may be slight, atypical temperature fluctuations, but high fever usually means a complication. Polyuria and polydipsia may occur. Rarely the cranial nerves are involved; the olfactory seems most frequently attacked and there are many cases in the literature where the sense of smell was weak or absent.

Mental symptoms may be prominent features of specific meningitis of the base. Apathy is the rule; the intense pain may cause a clouding of consciousness and the patient relapse into a stupor or coma; he may react, however, with an excitement. Sometimes stupid periods alternate with great excitement. A striking feature is to see these patients recover in a few hours from acute confusions or deep stupors and become practically clear mentally. Clinically too they may show mental pictures formerly classified as melancholia, mania, dementia, etc.

The prognosis of this condition seems to depend somewhat upon the early recognition of the cause and the intensity of the therapeusis. Mercury should be used and many syphilographers prefer the inunction method. It must not be forgotten in this connection that cases of choked disc, where the etiology is unknown, often show improvement under mercury.

Syphilitic Meningitis of the Convexity

Naturally this resembles a great deal the condition described above, with which it is often associated. The general symptom picture is, however, somewhat different, depending upon the localization of the pathologic process. In certain cases it can not be said absolutely whether the disease is of the convexity or of the base. It is as well perhaps to discuss here, once for all, the prognosis of cerebral lues in general, although it varies somewhat with the part of the brain invaded. Oppenheim[53] makes the general statement and Nonne agrees with him, that brain syphilis is a serious organic disease which frequently causes death, often leads to a chronic state, but also may end in

recovery. Its prognosis is decidedly more favorable than many other forms of organic brain diseases, e.g., abscesses, tumors, multiple sclerosis, or general paresis. The last two named end in death and, in the first two, while surgery is sometimes effectual, the results of a large number of cases are not such as to inspire optimism. It is difficult to give figures as so many cases obtain remissions of their symptoms and pass out of observation. Other cases too are reported as cures without any qualifying statement. The most reliable and painstaking statistics seem to be those of Naunyn and Nonne who report altogether 537 cases with 49 recoveries, that is, recoveries with no relapse after five years, a recovery record of 9 per cent. In these 537 cases partial recovery took place in 239 cases, or 44 per cent. Relapses are very frequent in cases thought to be cured. Nonne reports that in 56 cases which he observed for a period of three years, 22 relapsed once and 8 several times. Hence the hesitancy in calling any case recovered. The relapse may not take the form of the original attack; thus a meningitis may be apparently cured and after a year an endarteritis appear.

In considering the prognosis there are a number of individual features to take into account. Authorities disagree as to the influence of age. Hjelmann,[54] Naunyn,[55] Ricord and Fournier[56] believe that the older the patient the worse the prognosis, while Nonne does not think that such a dogmatic statement can be made. The length of time elapsing between the initial infection and the onset of brain syphilis seems to have some bearing; the observers mentioned above stating that the longer this interval the worse the prognosis. Heredity, according to Oppenheim and Nonne, has no bearing on prognosis. Any debilitating disease or condition has an unfavorable influence. Indeed Tarnowsky believes that where no such factor is present the prognosis is very favorable, but he is not borne out by the weight of authority. Head injuries do not appear to have nearly so much effect as has been supposed. The question of the bearing which the primary and secondary symptoms have on the prognosis of cerebral lues is a much debated one. However, the general opinion is that mild primary and secondary symptoms are more apt to be followed by syphilitic and parasyphi-

litic diseases of the nervous system and that these are more apt to be severe in their courses. Whether or not this is due, as some claim, to the fact that these mild secondary symptoms are not apt to cause energetic antispecific treatment, can not be definitely asserted as yet, owing to the absence of reliable data. Extragenital infection has no bearing on the prognosis.

To sum up the prognosis then we would say that: Sex has no influence. Prognosis is best between twenty and forty, somewhat worse between forty and fifty, and bad after fifty. Prognosis is bad if the infection occurs after forty. A neurotic make-up, a debilitating disease, or a head injury all influence the course unfavorably. Treatment of the first and second stages has no influence upon the prognosis. If the attack of brain syphilis occur in the first decade after the second stage, the prognosis is better than if it occur after that. The prognosis is the same in brain syphilis, spinal and cerebrospinal syphilis. The prognosis is better in cases which show no relapse.

The laboratory findings are as follows: The Wassermann reaction with the blood serum is positive in a slight majority of the cases; in the spinal fluid it is usually negative with 2 c.c., but becomes positive when larger amounts are used; very rarely it remains negative. The Nonne-Apelt, Phase I, is nearly always positive, usually strongly so. There is usually pleocytosis, the lymphocytes being somewhat increased.

The most common symptom is headache—in fact it is practically always present. It may be confined to one spot and often becomes worse at night. The severity varies and there is often tenderness on percussing the skull, this alone indicating a superficial disease of the brain. Pupillary anomalies occur rather frequently resembling those of general paresis, but differing in that they may clear up under antispecific treatment. Choked discs are not nearly so common as in the basilar form. Convulsions of the Jacksonian, or cortical type may occur; the convulsive seizures may be limited to one-half of the body, but more frequently they involve the whole body and are, in reality, an epilepsy. Sensory disturbances due to the cortical disease may be present, paresthesias, hyperesthesias, etc. More frequent are aphasias on account of the involvement of Broca's convolution in the disease process; these are usually temporary,

clearing up in from a few minutes to a few days. Monoplegias are fairly common. The prognosis in syphilis of the convexity is fairly good, in spite of the apparently serious nature of the symptoms. In fact, any form of localized meningitis has the best prognosis of any form of brain syphilis. In case of diffuse meningitis infiltration, however, it is much more unfavorable.

Cerebrospinal Syphilis

It is convenient for discussion to divide the various manifestations of syphilis of the central nervous system into clinical entities, although, as a matter of fact, the differentiation can seldom be made so clearly in practice. Thus some writers speak of cerebrospinal lues, others of the vascular types of cerebral lues, others simply of cerebral syphilis and general paresis, the latter being sometimes called the parenchymatous type of cerebral lues. Again cerebral syphilis is called a syphilitic disease and general paresis a parasyphilitic disease. By a parasyphilitic disease we mean, according to Head: "The expression of the reaction and necrosis of hypersensitized areas of the nervous system, evoked by the reappearance of the *Spirochaeta pallida.*" That is, the tissues have been so injured or altered by the earlier ravages of the disease germs that they react with great violence to small numbers of them or to small doses of their toxin. At any rate it seems generally admitted that there are at least two main types, which we will call cerebrospinal syphilis and general paresis. We shall deal with the former first.

By cerebrospinal syphilis we mean a syphilitic involvement of the brain and spinal cord, coming on soon after infection, showing chiefly a cerebral endarteritis and a specific meningomyelitis, accompanied by a multiplicity of mental symptoms and ending usually in death if untreated.

Cerebrospinal syphilis may come on at any time after infection—two months to forty years have been reported as the extremes—but it usually appears in from two to three years.

The symptoms are at first those of neurasthenia: headache, vertigo, insomnia, irritability, disinclination to work, etc.

Mentally the picture grows progressively worse. Dementia

may advance with startling rapidity. Some cases may show in every respect the so-called "typical" picture of general paresis and the two may be extremely difficult to distinguish. In fact the difference in the four reactions (*vide supra*) may be the only guide.

Either the spinal or cerebral symptoms may predominate, the others being comparatively mild or the disease may be evenly distributed. In some cases slight lesions in the brain may exist for years without affecting any important area, so consequently are not noticed, the transitory symptoms of headache, vertigo, etc., being ignored.

The neurologic symptoms are apt to be more in evidence than the mental ones. Palsies, mild and transitory in nature, are very common and should always give rise to the suspicion of cerebral syphilis. Monoplegias are frequent and there are temporary speech disturbances.

If the brain symptoms predominate, the symptoms most in evidence are headache, vertigo, epilepsies, mono- or hemiplegias and affections of the cranial nerves. Where the cord is chiefly involved, the symptoms are those of myelitis. In the former class of cases, however, the involvement of the cord is indicated by such symptoms as the loss of patellar reflexes and bladder disturbances, while in the latter case the coinvolvement of the brain is shown by pupillary anomalies, headache, vertigo, optic neuritis, etc. Where the brain and spinal cord are both about equally affected we have a combination of the two sets of symptoms.

The differential diagnosis is chiefly between cerebrospinal syphilis and general paresis, multiple sclerosis, tuberculosis, and multiple sarcomata and carcinomata of the leptomeninges.

As stated above there are certain clinical forms of cerebral syphilis where a grandiose mental state is very much in evidence that can hardly be distinguished from general paresis. In such cases we depend greatly on the four reactions and lately the Lange colloidal gold curve is thought to offer a superior diagnostic method (see above). Speaking generally, however, in cerebral syphilis the picture is neurologic rather than mental; the reverse is true of general paresis. In the majority of instances cerebrospinal syphilis develops within five years of the date of in-

fection, while paresis but rarely manifests itself until after five or more years have elapsed. Cerebrospinal syphilis is not apt to show the lengthy remissions that paresis does. Also the former condition may run a lengthy course and may end in recovery or in an arrested stage, especially if intensively treated, while paresis almost invariably ends in death in from one to five years after the condition is well established, even though energetic treatment has been employed.

Multiple sclerosis may resemble cerebrospinal syphilis in that for a long time it may show only the picture of a spastic dorsal myelitis. Multiple sclerosis may also, on account of the characteristic kaleidoscopic clinical picture imitate cerebrospinal syphilis in other ways, such as hemiparesis, external ocular palsies and the transitory nature of the symptoms. Multiple sclerosis, however, pursues a long, practically changeless course, and is not affected in the least by antispecific therapy. Moreover it commonly shows three symptoms which are rarities in cerebral syphilis; scanning speech, intention tremor, and nystagmus. The four reactions are also valuable diagnostic aids and the Lange colloidal gold curve is supposed to be negative, although a recent investigator has reported eleven cases of suspected multiple sclerosis, in seven of which—and the seven in which the diagnosis appeared most certain—curves resembling those of general paresis were found.

Tuberculosis of the nervous system may simulate cerebrospinal lues, in fact, the diagnosis may rest almost wholly upon a clinical differentiation between tuberculosis and syphilis, aided, of course, by the four reactions.

Sarcoma and carcinoma may be so generally distributed in the leptomeninges as to give rise to a clinical picture very similar to cerebrospinal lues. Siefert has reported several cases. Lumbar puncture is the chief diagnostic criterion.

General Paresis

This disease is also known as general paralysis of the insane (which is an objectionable term for several reasons), parenchymatous cerebral syphilis, dementia paralytica, and, by the laity, softening of the brain.

General paresis is a disease of the brain, always preceded by syphilis and usually occurring from five to fifteen years after infection, characterized by profound pathologic alterations in the brain tissue, accompanied by a diverse mental picture, tending to extreme dementia, and terminating in death, usually within one to five years, rarely longer.

The general tendency is to regard paresis as an incurable disease and, for all practical purposes, this is true. At any rate, in discussing the outlook with a patient's relatives, we are not justified in giving any but a very grave prognosis. However, while about one-half of all cases die within two years, and four-fifths of them within five years, most authorities are willing to admit that sometimes a case of general paresis occurs which does not result in death, or at least which runs along for such an extended period that death finally occurs from some accident. Thus Nissl reports a case of death after twenty-eight years and Alzheimer one which ran thirty-two years.

The etiology must be said to be syphilis, usually plus other factors. For many years there was a growing conviction that paresis always meant an earlier syphilis, the elaboration of the Wassermann reaction made this practically certain and the demonstration by Noguchi and Moore, in April, 1913, of the *Treponema pallidum* in paretic brains almost simultaneously with similar findings by Hough and Nichols, established the question beyond the doubt of any reasonable person. The question as to whether paresis is caused by the treponemata, or by the toxin, or by the hypersensitization of tissues by the long-continued presence in the body of the syphilitic virus is no longer debatable.

Many studies have been made of the incidence of paresis among various races, classes, etc., with the idea of determining whether or not there are other indispensable causes. With the establishment of syphilis as the etiologic factor *sine qua non* considerable of the fervor has gone out of this search. Alcohol has always enjoyed the reputation of contributing towards paresis. The formula written at one time by certain syphilographers was: syphilis plus alcohol equals paresis. It is now certain that paresis may occur in a total abstainer, but undoubtedly the abuse of alcohol by a syphilitic renders more probable

the occurrence of paresis. Paresis is much more frequent in men than in women, although this disproportion seems to be growing less. Occupation seems to figure only in proportion to the large incidence of venereal disease among certain classes —soldiers, sailors, commercial travelers, etc.—although some have thought that an occupation involving severe mental or physical strain, if continued for a great many years may cause paresis. It is undoubtedly true that certain races have syphilis, but are practically immune to paresis, which would seem to indicate a racial peculiarity—perhaps a tectonic or histologic peculiarity of cerebral structure—and would appear to be in harmony with the investigation made at this writing of the brains of paretics by an English observer tending to prove that there is a certain structural peculiarity of the brains of certain syphilitics which renders paresis probable. Also the well-known infrequency of the skin lesions in syphilitics who afterwards become paretics or tabetics certainly points towards differentiated strains of treponemata, one kind attacking cutaneous tissue, another nervous, and so on. Other factors are undoubtedly potent, as many facts prove, e.g., the fact that the women of lower classes are much more prone to paresis than those of the upper.

The pathology of paresis, in spite of the extensive and quondam authoritative studies of Nissl and Alzheimer, can by no means be considered settled. One thing is sure: the disease process is not confined to one part of the brain, or even to the brain itself. Besides a general involvement of the nervous system (including the medullary layer, the large ganglia, the cerebellum, the spinal cord, and the peripheral nerves), there is disease of other parts of the body, particularly the glandular organs, the liver, spleen, kidneys, etc. In the cerebrum there is an extensive disease process, especially of the cellular elements, with fiber atrophy. There is extensive new vessel formation, proliferation of the glia and plasma cells and lymphocytes are found in the vessel sheaths. Macroscopically when a paretic brain is examined the most striking feature is the adherence of particles of the cortex to the pia as it is stripped off, so that when this membrane has been entirely removed the brain presents a "worm-eaten" appearance. There is marked conges-

tion of the membrane and the cortex, often localized more prominently in one hemisphere and generally most marked in the anterior and middle regions of the convexity; there are distention and tortuosity of the pial vessels, the membrane itself is thickened and opalescent or milky; and tearing almost always occurs in separating the piaarachnoid. (Bannister.)[57] The vascular inflammatory changes in the acute forms may be most intense and in the so-called "galloping" paresis the basal finer arteries in the pons and elsewhere reveal a very marked periarteritis.

The nerve cells themselves show degeneration, although this is not so marked in the early stages; the fibrillæ of the ganglion cells are degenerated, especially within the cell body. Alzheimer says: "They are sometimes thickened, either from swelling or sticking together of several fibrils, or in short, heavy, broken pieces and fine granules disintegrated. There is no marked thinning of the intercellular fibril network and the destruction of fibrils appears to be more marked in the external layers than in the internal layers, and the very finest fibers are affected." These nerve cell changes are not especially characteristic, Alzheimer believes, the only degenerative changes peculiar to general paresis being a peculiar rotting of the processes and disintegration of the fibrils.

The nerve fibers also suffer and in the later stages of the disease the degeneration may involve the greater part of these in extensive cortical regions and be traced down to the basal ganglia and the medulla. There is quite commonly a peripheral neuritis in paresis and but few cases, Fuerster[58] says, have not involvement of the cord. In the tabetic cases the lesions may be those characteristic of tabes or primary degeneration of the posterior root fibers and posterior column sclerosis, but the spinal cord tracts affected need not be and are not always the same as those in tabes.

The neuroglia is affected in that there is proliferation of the spider cells, the tangled-up processes of which present a characteristic appearance especially where the normal nerve cells have disappeared, as is so often the case in the internal and external limiting layers of the cortex. The cortex itself may shrink to one-half its normal size. Along the vessels appear elongated rod cells of glial origin. According to Alzheimer, the

most significant microscopic picture in paresis is a general perivascular infiltration with plasma and rod cells.

When we come to discuss the symptoms of general paresis we find the chief difficulty is that of presenting a fairly accurate, clear picture in a reasonable amount of space. Besides the well-known "grandiose" paretic who typifies the disease for so many physicians, but who comprises in reality only one-fourth or one-fifth of all cases, there is a bewildering number of patients presenting diverse mental pictures. These will not confuse so much, however, if we bear in mind the fact that they are all linked together by a fairly constant neurologic and laboratory picture and run a common downward course. For descriptive purposes the disease may be divided into three parts:

The early stage of general paresis is often well under way before it is recognized. The mental symptoms may be quite insidious. Patients sometimes develop a neurasthenic picture, they are easily fatigued, absent-minded, hesitate to undertake tasks, have headache, vague pains, insomnia, etc. The first symptoms noticed are sometimes neglect to keep important engagements, loss of keenness, inattention, failure to grasp details, etc. These are particularly noticeable if the patient fills a position requiring close attention to details. Some patients become dreamy, fall asleep at work, or give the impression of being mildly intoxicated. Paretics have indeed been arrested on this suspicion by too zealous police officials. Other patients become happy, busy, full of projects, exhibit an activity like hypomania, engage in new business ventures, disregard established habits of thought and action and spend money recklessly. Slovenliness of attire and deterioration of conduct are significant signs. The careful dresser comes to breakfast without a necktie, the staid business man is seen reeling home from work, and the pillar of society consorts with prostitutes in a public restaurant. The careful, pecunious man, who has hoarded a few thousand dollars at great self-sacrifice, squanders it in a few days in silly schemes. A street car conductor in the writer's practice had saved $800 in about twelve years of scrimping by himself and his wife; he began to spend this and in a few weeks had purchased a lot of new furniture, furs and jewelry for his wife, had made a payment on a grand piano and had bought a few pigs to keep in his

(city) back yard. Careful mental examination of patients even in the earliest stages, when the man on the street would be able to find nothing wrong with them, reveals difficulties in association, lessened capacities for learning, disturbances in attention and loss of memory for recent events. As the disease progresses, memory defects may be very striking, the date of marriage is forgotten, the age of the children, etc. The patient is happy, easily pleased, full of plans for the future and unable to appreciate his condition. He hears the physician tell his wife in his presence that his case is hopeless and is not affected in the least; he talks to the doctor for a time and then thanks him profusely when he has received neither medicine nor advice. These patients are as a rule easily influenced, especially by strangers, and may be persuaded to give up their money by crooks or to enter an asylum by physicians with equal facility. It must not be forgotten also that there exist melancholic types; a mild depression which is diagnosed as neurasthenia or manic depressive may constitute the picture. As the disease progresses the impairment of the intelligence and memory become more marked, patients forget a meal just passed, a recent visit, their birthday, the number of their children; they are unable to do quite simple mental tests, but with it all exhibit a great good humor, suggestibility, and entire lack of appreciation of their condition. A group of such patients may be presented to an audience of students who are told without any pretence of concealment that they are suffering from an incurable disease from which they will die inside of a few years. They listen or appear to listen to their pronounced doom with the greatest affability and laugh and joke with the students. Their delusions may become fantastic in the extreme: Gargantuan ideas of wealth, power and grandeur arise. They think in Olympic terms, their wealth is reckoned by the billions, they have a million wives and countless children, a chest of iron, an arm of brass, their urine is wine, their feces gold, they can lift a house, never sleep, and armies move at their command. Their delusions shift about, vanish, reappear and expand or contract at a suggestion or a question. This is the so-called "typical" paretic and in the days before the refinements of laboratory diagnosis was thought to represent the bulk of such patients. It would be well, however,

for the physician to bear in mind rather the other types of the disease; the grandiose paretic is easy enough to recognize, the difficulty is in the large number of cases showing only a slight dementia or a depression.

The above symptoms occur in the first stage of the disease which has been arbitrarily defined as extending from the onset to the first convulsive seizure. This scheme of dividing general paresis into three stages, before the convulsions, convulsions, and the soiling or the wet and dirty stage, has no scientific quality to recommend it and is only warranted as a descriptive method if we bear in mind that these stages are seldom clear-cut, in fact, may be varied indefinitely. Thus we may have the disease ushered in with a convulsive seizure, we may have a patient bedridden for months, apparently about to die, and then have a remission and go through the entire course again, and then again we may have no convulsions.

Convulsive seizures are, however, the rule. They may occur at any time during the disease, but it is quite common for them to come after a period of relative mildness and to be followed by a more serious stage. Often convulsions usher in the bedridden stage, or perhaps death occurs during a number of them. These convulsions may be epileptiform or apoplectiform in type but as a rule are rather easily differentiated from epilepsy or apoplexy. Convulsive seizures occurring for the first time in middle life should always make the practitioner suspect paresis, especially if they are followed by a paralysis which only lasts a day or two. They are often preceded by definite prodomata, twitchings, a dreamy state, thickness of speech, etc.

The so-called second stage of the disease is marked by such an increase in the symptoms that the disease becomes patent, even to the layman. Speech is thick, even unintelligible, ideas of grandeur come and go, the patient is happy, boastful; he is slovenly in dress, neglects to wash, put on a collar or tie, lace his shoes, or button his trousers; he urinates where he happens to be, uses vulgar and profane expressions freely, can not fix his attention on anything, is greedy and lustful. Judgment is practically nil—these patients are swayed by the impulse of the moment. Kraepelin tells of one who stepped out of a second story window to pick up a cigar butt he noticed on the side-

walk. Stealing is done in an open way, the paretic may walk into a store, help himself from the counter and walk out; sexual misdemeanors are frequent.

The third stage of the disease is said arbitrarily to begin when the patient soils himself. As an illustration of the failure of the laity to appreciate obvious mental symptoms may be mentioned the case of a cashier who was only suspected of being ill when he was soiling himself regularly while at work. He had been holding down his position, which was such that no especial check was kept on him, and it was found that he could not do the simplest sums, and made errors in change constantly. Following the loss of control of the sphincters the course is rapidly downward. It is best to care for the patient in bed. Plenty of good, wholesome food and scrupulous cleanliness are the nursing desiderata. Mentality often diminishes to the extent that these patients become no more than vegetables: they take food and expel excreta and that is all. Many, however, retain fragments of a grandiose delusional field to the end. It is a pathetic sight, indeed, to see a bedridden paretic, reduced almost to a skeleton, awaiting a certain death, smile at the physician and say he feels fine. There is often such disease of the sensory nerves or their central neurones that pain is practically impossible. The writer knew a paretic who fell, breaking his femur completely in two. In spite of all care he would tear off all the dressings from time to time and *walk about the ward* on the broken bones. Strange to say, union with a large callus occurred. Constant nursing care is needed to prevent bedsores in these cases. In the dark ages of insane asylums the spectacle of a number of bedridden paretics was truly horrible. The patients were ghastly simulacra of human beings, had an unthinkable stench about them and often exhibited gaping holes of rotting flesh on their backs, with the coccyx, sacrum, and iliac bones exposed to view. Nowadays, however, more humane and intelligent care of these cases has resulted in a much different state of affairs.

The laboratory signs of general paresis have been given above. The physical signs are numerous and variable. There are four, however which should be ever borne in mind as they constitute an easily-remembered, easily-applied, diagnostic compendium.

They are the speech defects, the Argyll Robertson pupil, the abnormal knee reflex, and Romberg's sign.

The pupils should be examined carefully for inequality of the two, unevenness of outlines, and disturbances of reaction to stimuli. The normal pupil is slightly below and to the inner side of the center of the iris, is round and has a regular contour. Any change in the light causes a perceptible change in its diameter, increase of illumination causes a contraction and decrease a dilation; this is the direct reflex reaction to light. When one pupil is kept covered and the other exposed to the light, the covered pupil also contracts almost as much as the exposed one; this is the consensual or the indirect reaction. In general paresis pupillary anomalies are extremely frequent. Inequality of outlines of the two pupils occurs in about two-thirds of all cases, irregularity of outlines in about three-fourths and the Argyll Robertson pupil in something over half of all cases. The loss of the consensual reflex is one of the earliest and most persistent of all the eye symptoms. The complete Argyll Robertson pupil is one which reacts to accommodation and remains fixed to light. According to Kraepelin,[59] a persistent Argyll Robertson pupil means syphilis of the central nervous system. Too much care can hardly be used in examining for it. The sympathetic reaction of the pupil is tested for by slightly scratching or tickling the skin of the neck in front of the ear below the angle of the jaw. Normally this causes a dilation of the pupil: it may be lost in paresis.

Romberg's sign is a test for coordination and equilibrium. The patient stands erect with feet together and shuts his eyes tightly. If the sign is positive he sways or even falls, if not supported.

The examination of the speech should include a survey of his ordinary speech together with the application of special test words or phrases. Sometimes difficult words are pronounced correctly when the patient concentrates on them, while he stumbles over easier words in ordinary conversation when he comes upon them unawares, so to speak. Some favorite test words are such as "Methodist Episcopal," "hippopotamus," "perturbation," "3rd riding artillery brigade," etc.

The deep reflexes are usually exaggerated in general paresis, rarely diminished, or absent. Diminution or loss is more sig-

nificant, however. The knee reflex is the most easily elicited. Seat the patient in a chair with his knees crossed, the upper leg swinging loosely. Distract his attention in some way and tap the tendon of the quadriceps sharply just below the knee, this causes an extension of the leg. If the reflex is exaggerated the foot kicks out promptly to its fullest extent.

The above four symptoms are mentioned as a brief, easily-utilized examination of the suspected paretic in the physician's office, but there are a multitude of other symptoms. Sensory symptoms are frequent, such as disturbances of skin sensation, numbness, itching, etc. There may be an absolute inability to feel pain. Motor symptoms are incoordination, ataxia, apraxia, adiadochocinesias, etc. Babinski is common, together with Chaddock's sign and Gordon's reflex. In the final stages contractures are the rule and these bedridden cases may show spasms, atrophies,—all sorts of neurologic symptoms.

The diagnosis of general paresis as a rule presents little difficulty to the neurologist or psychiatrist, but there are cases which resemble so closely other conditions that a careful study of the cerebrospinal fluid findings, taken with the course of the disease and the autopsy may be necessary to establish the diagnosis beyond a question. If we dismiss from our minds the picture of the exalted, grandiose paretic and remember that the mental symptoms may be almost anything, we shall miss fewer cases. Alteration in the habits of a middle-aged person should rouse our suspicions and especially wherever we know a patient has syphilis we should be on the *qui vive* for paresis. On the other hand certain conditions, especially chronic alcoholism, may simulate the clinical picture of paresis very closely. Only by the laboratory signs, as given above, can we make an absolute diagnosis. When the four reactions of spinal fluid are positive, particularly when a small quantity of the fluid—0.05 to 0.2 c.c—is used for the Wassermann, we are practically certain of paresis.

The prognosis is fatal for all practical purposes, although Nonne has this to say: "It had previously been considered that a genuine paresis is incurable, but this opinion can not, at the present time, be unqualifiedly maintained." Certainly there have been long remissions where death has intervened from other

causes before a relapse occurred. Nonne, in a vast number of cases, has seen four which he calls recovered.

Then there are the cases of Nissl and Alzheimer (*vide supra*). Every alienist is familiar with cases of long remissions which make him chary of being too dogmatic with a patient's relatives. It is embarrassing to tell a paretic's wife, for example, that he is certain to get steadily worse and die within a few years and then have him get well, to all appearances, and remain so for an indefinite time. It is practically impossible, moreover, to convince the relatives of a patient in a remission that the disease is only in abeyance. The disease runs its course in the great majority of cases within three or four years, rarely five or six years, and very rarely over six years, but a very small percentage of cases may last ten years. On the other hand there are cases which might be called "fulminating" where the disease hurries through its course in three to six months. It is quite common for the patient to die in from one to two years after the onset.

The possibility of remission must never be forgotten, especially in dealing with the patient's family. These are by no means infrequent, occurring to some extent in about one-sixth of all cases. Very long ones have been reported, even five or six years, but the usual time is about six months. To the uninitiated the patient may appear completely recovered in one of these remissions and, unfortunately, they are too apt to be regarded by their relatives as entirely well and given control of property with perhaps disastrous results. Only a close scrutiny of the patient from all three viewpoints, the physical, the psychical, and the laboratory, betrays the presence of mental disorder. No matter how near death the patient may appear there is a possibility of a remission.

Many treatments have been advocated for general paresis, the most important of which are given above. Some syphilographers hold that while intensive treatment may mitigate the symptoms temporarily, it shortens the patient's life. At the present writing a combination of the judicious use of mercury with the Swift-Ellis method of giving arsphenamine is the treatment of choice. There are many cases reported in the literature recently which have shown apparent recovery under this, or a treatment resembling this; some of these have not shown a relapse,

although four, or five, or even six years have gone by. It may be then that we are on the verge of conquering this scourge. Time alone will tell. It should be mentioned, however, that statements from authoritative sources have been made alleging that the intravenous mode of administering salvarsan is more convenient, less dangerous, and every whit as effective as the Swift-Ellis.

Whatever decision is reached in the individual case about antispecific treatment, other features of the case should not be neglected. The first of these is legal sterilization. By this is meant the deprivation of the patient of all legal rights so that he may not squander his own or his family's resources, as has so often happened. This step should not be delayed a day after the diagnosis. The patient himself should be kept under strict survey, which means an institution in most cases. Regular regime and good hygiene are important. Much can be spared the patient and his family in suffering by the careful, intelligent nursing care of these cases.

Before leaving the subject of paresis at least three variations or modifications of the disease should be mentioned. *Lissauer's type,* a name given to irregular forms which show hemiplegia, and spastic paralysis of various kinds, an endarteritic form, and syphilitic pseudoparesis.

Taboparesis properly belongs under this head; clinically it might be called a mental paresis and a neurologic tabes, but pathologically it seems to be something rather more than paresis with the disease processes predominating in the cord. The laboratory signs have been given above. Clinically taboparetics may show any of the mental pictures of paresis proper, but it is usual for the symptoms to show an onset less pronounced and for the disease to run a longer course. The characteristic symptoms are hypotonia of the legs, lightning pains, visceral crises, arthropathies, the ataxias, and the loss of the patellar reflexes.

Juvenile paresis is simply general paresis occurring in a child or youth as the result of syphilis acquired at or near birth. The usual age of occurrence is from seven to twelve years and there is usually a simple dementia, deepening rapidly, rather than the richly delusional picture of the adult, undoubtedly because the child has not had the time to lay in such a store of

association, imagery, etc. Formerly many of these cases were called epilepsy or imbecility, but since the Wassermann-Plaut technic more of them are being recognized. They run a course of three to four years, ending in death. Remissions are rare and we know of no recoveries in the literature.

Tabes

In any attempt to review the history of tabes we at once come to the discovery that there are really three distinct histories. There was a disease or rather a rough collection of symptoms called by that name, which had its initial recognition in the Hippocratic Era and was described from then on down until the sixteenth and seventeenth centuries. This embraced all kinds of discharges from sexual organs—spermatorrhea, gonorrhea, leucorrhea, gleet, etc.; while if the cord were diseased, as in any form of myelitis, or Pott's disease, the title given was *tabes nervosa.* The clinicians of the sixteenth and seventeenth centuries began to approximate the real tabes, however, by excluding the venereal discharge, although they included all sorts of paraplegias in the term. The sexual idea was by no means lost, however, and even down as late as the beginning of the nineteenth century the term was applied to sexual weakness or "sexual neurasthenia." At about this time, however, the real tabes began to separate itself out of the confused mass of clinical material, and during the first half of the nineteenth century there were a host of investigators hacking away at the problem, until the real tabes began to take shape. W. Horn, Decker, Romberg and Steinthal may be mentioned as prominent among these early observers, but it was Duchenne, in the sixth decade of the nineteenth century, who put the finishing touches to the picture and gave a fairly satisfactory account of tabes dorsalis as we understand it. The history since that time is too full of names to quote them here. Those interested should see the historical accounts of Jelliffe,[60] Schaffer,[61] Lewandowsky and Massary.

The frequency of tabes may be said roughly to be one-half that of general paresis. About three to five in every hundred syphilitics develop the disease and the ratio of men to women is

variously given as from four to one, to ten to one. It must be mentioned that in many countries where syphilis is common, tabes is rare. It also seems to be very rare among prostitutes. In 1916 Lucke[62] studied 250 cases of tabes and compared his results with similar statistics. He found that the average period of beginning tabetic symptoms after the primary sore was 15.34 years. He found 82.8 per cent in white males, 11.6 per cent in white females, 5.2 per cent black males and 0.4 per cent black females. The incubation period varied from three to forty-five years.

Syphilis is the only cause of tabes. This is admitted by the leading authorities today. The honor of the discovery belongs to Fournier,[63] who advanced it in 1875, but it was not until the days of Wassermann, Plaut, *et al*, that it was established. Nonne and other authorities agree that the syphilitic origin of tabes is established beyond a doubt. A great number of other causes have been assigned as contributory, even, some say, essential—exposure to cold and wet, trauma, excessive venery, etc. Heredity has been stressed by Charcot and Erb.

The pathology of tabes is, speaking roughly, a sclerosis of the posterior columns of the spinal cord. Even with the naked eye the cord is seen to be atrophied, especially posteriorly; this atrophy is more marked in one place than another, being more pronounced in the dorsal and sacrolumbar regions. Meningeal involvement is very frequent. Under the microscope there is a leptomeningitis, resembling a syphilitic meningitis, but not so severe. Lymphocytes and plasma cells are found in the pia and arachnoid. The characteristic changes of the disease are found in the posterior columns and roots. There is a degeneration of the posterior columns varying in extent, and usually more marked in the region of the posterior horns. The posterior roots show pathologic changes as do the ganglia of the sympathetic system. The neuroglia is increased, with subsequent sclerosis. The Gasserian ganglion may be involved, as may the proximal root of the 5th nerve. Degeneration of the optic nerve sometimes occurs. There may be degenerated fibers of the peripheral nerves.

There are several explanations of the peculiar pathology of this disease, but we will only mention two, Strümpell's and

Marie's.[64] Strümpell held that syphilis may produce a toxin which has an injurious effect upon the ganglion cells and nerve fibers of the nervous system. This toxin has a selective action on the sensory portion of the cord just as ergot, or as lead has on the motor tracts. Marie and Guillain claimed that tabes was a syphilis of the meninges, attacking chiefly the posterior part of the pia. In the pia, they said, there is a lymph system by which the disease process is extended to the posterior part of the cord. Strümpell's theory is the one generally held; the majority of authorities reject Marie's as being ingenious, simple, but, as the Scotch say, not proven.

The symptomatology of tabes is a large and confusing subject, but there are seven cardinal symptoms which the practitioner would do well to bear in mind to orient himself on the subject. They are lightning pains, loss of tendon reflexes, girdle sensation, visceral crises, Argyll Robertson pupil, ataxia, Romberg's sign and bladder disturbances. Lancinating or lightning pains occur, according to Baldwin Lucke in 88.4 per cent of all cases, loss of knee jerks in 90 per cent, girdle sensation in 31.2 per cent, visceral crises in 12 per cent, Argyll Robertson pupil in 80 per cent, ataxia of legs in 87.2 per cent and of arms in 68.2 per cent, Romberg's sign in 96.4 per cent, and bladder disturbances in 67.6 per cent.

The Romberg's sign and the Argyll Robertson pupil have been discussed above and need not be dwelt upon except to say that before the Romberg sometimes the patients are unable to balance themselves on one foot and the Argyll Robertson pupil may be present for years without other symptoms.

The lightning pains are often the first symptoms noted; the patients complain of severe, fleeting pains, especially in the sciatic region. They come on in attacks which may last only a few minutes, or a few hours, or perhaps several days. Sometimes they are the only symptoms of the disease in evidence for months or years, and are apt to be called "neuralgia," "sciatica," or "rheumatism." These pains which are due to the attack of the syphilitic toxin on the meninges, are very acute and cause the patient extreme agony at the time and apprehension between attacks.

Associated in nature with these lancinating pains are the vis-

ceral crises; the best known are the gastric. A gastric crisis begins suddenly with violent pains in the stomach, often there is nausea, vomiting, and great prostration. They last a few hours and disappear suddenly. They are extremely liable to be called "gastralgia" or simply "acute indigestion." Similar crises of almost any other organ may occur, the intestines, the kidneys, etc. What seems to be renal colic should always be suspected of being a tabetic crisis.

Among the initial symptoms is the diminution or loss of the tendon reflexes, especially the knee and Achilles. Often one knee is affected long before the other. The same is true of the ankle.

The girdle sensation, on which so much stress was formerly laid, belongs to the picture of sensory involvement. Often, before it is felt, the patient complains of numbness, a tingling or crawling sensation, particularly on the soles of the feet and the palms of the hands. The patient may say he feels as though he were walking on a carpet, or wearing a glove. Flashes of heat and cold may be present.

The gait disturbances are very characteristic. First the patient complains that he can not get up and down stairs comfortably; he feels insecure when he walks over uneven surfaces. This is more noticeable at night. Then he takes to a cane and gradually develops the tabetic gait, to see which once is worth a page of description. The legs are wide apart, the knees overextended and the feet brought to the ground with a stamp, heel first. Finally he can not walk unless reeducated (see under treatment, below). The ataxia in the arms is noted in writing, buttoning clothes, etc.

Weakness of the bladder is quite common, causing incontinence; cystitis may develop. Sexual desire is usually lost, sometimes increased. Constipation usually occurs, sometimes fecal incontinence.

The above symptoms are usually more than ample for an early diagnosis. Other symptoms may be found on careful investigation. Thus the pain sense may be lost in irregular areas. Heat and cold sensibility and bony sensibility may be absent or very much diminished. Any or all of the cranial nerves may be involved. Optic atrophy is frequent. Trophic symp-

toms are common, especially arthropathies. Charcot joint and perforating ulcers of the foot will be seen in a certain percentage of cases (9.2 per cent and 3.2 per cent respectively).

The diagnosis is not difficult. Aside from the host of clinical symptoms there are the blood and cerebrospinal fluid findings (*vide supra*). An alcoholic polyneuritis is sometimes confusing, but the laboratory findings mark the difference. When syphilis exists with alcohol diagnosis is more difficult, especially when a clinical picture resembling tabes has been caused by the alcohol and when the syphilis causes anomalous serologic findings. Diagnosis is very difficult in these cases, which are fortunately extremely rare. Withdrawal of alcohol and energetic, antispecific treatment will cause a subsidence of the symptoms, but naturally this has no effect on true tabes.

What has been said about ease of diagnosis should not lead to overconfidence.

Nuzum,[65] in 1916 reported twenty operations on tabetics under mistaken diagnosis. The usual operation was laparotomy for gastric crisis, the diagnosis made being gastric ulcer, gall bladder disease, and appendicitis.

The prognosis in tabes is very poor. Exhaustion may occur from the disease itself, causing death, intercurrent disease may carry the patient off, or various accidents, such as choking, aspiration pneumonia, etc. may occur. Cases are believed to be arrested and remain so for years, but the newer serologic methods have not yet been in use for a long enough time to verify this. However, it is known that the course is much longer than paresis, extremes of six months to thirty years have been reported and the average duration is ten to fifteen years.

The treatment falls into three parts, antispecific, nursing, and reeducational. The antispecific has been given above. It should be instituted as early as possible and persisted in. Even when the symptoms have entirely disappeared we must not feel safe. Relapse always threatens: "Syphilis does not die, it only sleeps."

One important quality of the treatment of tabes is its timeliness. This depends upon the earlier recognition of the character of pains which are called rheumatic, gastric, vesical,

urethral, renal, autotoxemic, and so on, rather than tabetic. Prophylaxis of course is the treatment *par excellence;* first, prevention of syphilis itself and, second, prevention of the accessory factors of Strümpell, alcoholism, toxemias of various kinds, sexual excesses, exposure, and trauma.

In the actual treatment of the tabetic process preference must be given to arsphenamine therapy and the best results are obtained by the intrathecal injection by the Swift-Ellis method. This is indeed what one would expect on theoretic grounds, considering the pathology of tabes. Dividing tabetics into two classes—those which show an active process and those which do not—we may say that arsphenamine is indicated only in the former class of patients, but this rule has many exceptions (Nichols). Speaking generally, it may be said that the arsphenamine therapy of tabes offers more certain, rapid and definite results than any other (Jelliffe). Some of these results are as follows: The pains and bladder symptoms—after a temporary aggravation for which the patient must be prepared—clear up remarkably; so much so that this alone almost justifies the treatment. The ataxia has been very much improved. The Argyll Robertson pupil and pupillary irregularities have disappeared. (Optic atrophy and the so-called Herxheimer reaction are believed now to be due to insufficient arsphenamine therapy.) External and internal ocular palsies, impotence, visceral crises, loss of memory, anorexia, and general weakness have all shown marked improvement with arsphenamine.

Neisser recommends the hypodermic injection of mercury for tabes. Erb favors mercurial inunctions as does Sarbo, especially in the treatment of ocular palsies. This is also the basis of the famous "Aachen" method, combined with sulphur water. A usual course is to begin with 3 to 4 grams of mercury ointment, increasing gradually until 30 to 40 grams are used; the formula is six days' rubbing and one day's hot bathing. If the mercury is well borne the amount of ointment may be increased until 120 to 160 grams are used daily. Then potassium iodide is given in 1- to 1½-gram daily doses for six to eight weeks, when a new course of inunctions, using 120 to 160 grams of the ointment, is instituted.

A number of salicylate preparations have been recommended and have their champions; enesol may be cited as a good ex-

ample of these. It may be given in doses of 2 c.c. every other day for from 20 to 30 doses, injecting them intramuscularly. The biniodide, the bichloride, the cyanide, and the benzoate of mercury, all have their advocates, but probably the salicylate is to be preferred to any of these, except in these rare cases where there exists an idiosyncrasy for it. The biniodide of mercury has also been given directly into the subdural spaces, for the sake of having it act directly upon the posterior roots, and collargol, fibrolysin, and electromercurial have also been used in the same way. Sicard and Cathelin have given epidural injections.

Besides the medicinal treatment, other forms of therapy have been recommended—hydrotherapy, massage, mechanotherapy counterirritation, surgery and reeducation methods. Hydrotherapy has a limited use, but is not all that the literature sent out from various watering places would have us believe, certainly it is not curative. Hot baths of short duration may relieve pain, and intelligent hydrotherapy, combined with antisyphilitic therapy, may result in more rapid improvement than with the latter alone. Massage has a limited usefulness, chiefly as a passive exercise in bedridden cases. Mechanotherapy, in the form of suspension and osteopathy, seem to help only in proportion to their psychic effect. Counterirritation may have a very beneficial effect on such symptoms as the pains; if the skin is healthy, blistering the skin over a root zone responsible for the sensory symptoms, may give great relief. It should not be used, however, except in a case which is well under control and should only be regarded as a symptom-relieving adjunct to regular treatment. Electricity in tabes has sunk from a position of high esteem to a bare toleration as an occasional means of relief in obstinate pains.

Surgery in tabes has a definite, if small place. The arthropathies, for example, are surgical conditions. In 1888 Bennett and Dana first suggested severing the posterior roots in intolerable pain in tabes which resisted other treatment. In 1912 Singer published 38 such operations, most of which were successful in relieving the pains. O. Forster has had considerable success in his treatment of persistent gastric crises by severing the posterior root, thus doing away with the irritation of the sen-

sory-sympathetic gastrointestinal fibers. Careful and accurate neurologic examination is essential in order that the exact sensory fibers involved shall be determined and only the corresponding sensory roots sectioned. The nursing treatment for tabes includes careful cleanliness and constant watching for the first signs of decubitus. The bedridden cases require especial care.

The ataxia of tabes, if allowed to progress, will have its logical result in the complete inability of the patient to walk so that he becomes bedridden. That this ataxic process can be treated and the patient taught to use his limbs again by a re-educational process was advanced by H. S. Frenkel in 1902 and since that time his method has gained universal recognition. It is impossible to present his treatment briefly. Any physician who is called upon to treat a case should consult Frenkel's book.[66] The principle of it he states as: "The treatment of tabetic ataxia is based upon the education of the central nervous system by means of repeated exercises which enable it to receive sufficiently distant stimuli from the limbs as to their position and so on, although the available quantity of sensation is rather small."

In treating gastric crises cerium oxalate in 1- to 5-grain doses three times a day or cocaine hydrochloride gr. $\frac{1}{6}$ three times a day may be tried. A severe crisis will usually require some form of opium, and there is nearly always danger of acquiring an addiction. When the attack is nearly over sumbul may be given in $\frac{1}{2}$ drachm doses and after the attack a tonic of iron, arsenic, etc. Tabetic neuralgias are treated in a manner not dissimilar to other neuralgias. The lancinating pains require luminal, novaspirin, or similar remedies.

Syphilis of the Spinal Cord

This may be acute or chronic; the chronic form may become acute at any time. Acute specific transverse myelitis is not so uncommon. Orlowsky, in 72 cases of spinal syphilis, found the acute type in 19 cases. Nonne in 212 cases only reports eight. The combination of these figures makes it seem that about one case in ten of spinal syphilis is that form. The etiology is, of course, syphilis. What causes the disease to choose the spinal

rather than the cerebral form can not be said. In fact, some writers hold that there is no great distinction between the two forms, that it is all cerebrospinal syphilis, in one case with the brain symptoms predominating and in the other with those of the cord.

The pathology shows a well-marked meningitis, with sometimes gummatous processes. There is specific disease of the blood vessels, and inflammatory infiltrations around them.

The characteristic symptoms are meningeal in origin. Severe shooting pains occur in the region of the scapula, the neck and hips, also darting down the arms and legs. These pains may be preceded by paresthesia. The cord becomes reflexly excitable, evidenced by increased knee jerks. When gummata exist, pressure symptoms are found, indistinguishable from a tumor of the cord. Where the posterior roots are chiefly involved we have marked disturbances of sensation. Many neuralgias belong to this class. About one-half of all sciaticas, some authorities say more, are due to syphilitic radicular disease. When the disease takes the form of a transverse myelitis we have a paraplegia, flaccid of course, the bladder and rectal functions being impaired. Many combinations may be found—the involvement of certain tracts to the comparative exclusion of others may give rise to symptom-complexes resembling Brown-Sequard, poliomyelitis, primary lateral sclerosis, etc.

The diagnosis may be extremely difficult. A complete history of the case, minute neurologic examinations and serologic examinations of the spinal fluid are usually necessary. Tuberculosis, malignant tumor, spinal apoplexy, as well as practically all the cord syndromes must be differentiated.

The prognosis appears to be rather poor. The well-developed type usually runs a rather rapid and fatal course. In the completely paralyzed, cystitis and decubitus are frequent occurrences and hasten death. Even in these cases careful nursing attention may prolong life greatly.

Most authorities agree, however, that early diagnosis and energetic, persistent treatment make for a good prognosis. Oppenheim believes that the outlook is not as good as in cerebrospinal syphilis. Prognosis also depends upon the condition of the patient in other respects. Advanced age, existing disease in other

organs, alcohol or any other intoxication makes for a poor prognosis. The form of the disease has much to do with it. If the chief pathologic process is a transverse myelitis or a chronic myelitis, paralysis due to small-celled infiltration of the meninges and gummous infiltration into the cord and membranes, the outlook for recovery is not bad. Even complete cure may occur, or there may be left some paresis of the legs together with certain neurologic signs, e. g., the knee-reflexes may remain absent. A lesion of this sort is more dangerous when in the lumbar or sacral cord than in the dorsal on account of the paralysis of the bladder and rectum as well as the tendency for bedsores to develop. Any involvement of the medulla is very dangerous. The prognosis is not affected at all by the amount of treatment which the syphilis has had before spinal syphilis develops.

The treatment does not differ markedly from that of cerebrospinal syphilis. Early recognition, energetic antispecific treatment and good nursing care are the main requirements.

Syphilis of the Peripheral Nerves

Since Ballen, in 1663, and Cummius, in 1684, described facial spasms and eye palsies much has been written on syphilis of the nerves. There is no doubt that some involvement of the peripheral nerves is very common, perhaps almost universal, in syphilis. A great many of the neuralgias which bring patients to physicians on account of their intensity, persistence and tendency to recurrence are found to be due to this cause.

The cause may be an actual invasion by the syphilitic virus of the nerves themselves or they may be compressed by gummata, enlarged lymph glands, etc. The nerve sheath may become infiltrated, causing an epi-, peri-, or endoneuritis. The syphilitic toxin seems also capable of causing a specific neuritis, although just how this is brought about is doubtful.

The pathology is various. Where the neuritis is indirectly produced, there is nearly always an atrophy due to pressure, as, e. g., when a nerve runs along a bony groove. In direct disease of the nerve there is involvement of the nerve itself and infiltration of the nerve-sheath, giving a perineuritis which, as the disease process progresses, causes epineuritis and endoneuritis

as irregular, cone-shaped projections develop on the nerve sheath, causing pressure against the axis-cylinder. The nerves may also be primarily affected with the gummous type of syphilis.

A "syphilitic root neuritis" may occur. In this the anterior and posterior roots of the cord, especially in the cervical and dorsal lumbar regions develop cylindrical enlargements occurring in rows like beads. The peripheral nerves may develop a similar picture. This can be observed by palpating a peripheral nerve with the finger. Whether or not a simple specific degenerative polyneuritis may occur is a mooted question. There is nothing to prove that it can; but clinically we observe a polyneuritic picture in syphilitic patients, which is cleared up by antispecific treatment.

There are four varieties of peripheral nerve syphilis, the neuralgias, neuritides, polyneuritides, and root neuritides.

A neuralgia may occur in almost any region of the body, but facial neuralgia is the most common, those occurring in the region of the lumbar and sacral plexuses next. These latter are responsible for many cases simply called "sciatica." Neuralgia of the cervical plexus is not uncommon, neither is intercostal neuralgia. It is rare of the brachial plexus. The symptoms are severe pain, coming on suddenly, with tender spots along the nerve on pressure.

The symptoms of syphilitic neuritis are those of any other form of neuritis. Paresthesias are common and sometimes severe pains in the region supplied by the nerves. Nodular swellings of the nerves are found on palpation. A flaccid paresis or paralysis of peripheral character is found, and some atrophy. Rarely a single nerve is affected, usually several nerves. Polyneuritis is more common. The paresthesias, etc., are then widely distributed, as is the motor weakness and atrophy.

Specific root neuritis has been well described by Kahler. A stealthy progressive paralysis, of peripheral character, attacks the cranial nerves one by one. A slowly increasing neuritis appears in the region of the spinal nerves, accompanied by hyperesthesia or a girdle sensation or girdle pain as a consequence of progressive disease of the posterior spinal nerve roots.

The diagnosis may be quite difficult; e. g., between a slowly developing root neuritis and a malignant tumor of the vertebræ

and meninges in a syphilitic the distinction can hardly be made. A neuralgia, neuritis, or polyneuritis developing in a syphilitic showing the symptoms given above and yielding to antispecific therapy does not present so much difficulty.

The prognosis, with adequate treatment, is good for recovery, but relapses are frequent. Improvement is often surprisingly rapid.

The treatment is, of course, energetic antisyphilitic measures, coupled with good hygiene. Severe exacerbations of pain require coal tar products, or even opium.

Syphilis of the Cranial Nerves

Involvement of one or more cranial nerves is a quite common condition in syphilis of the central nervous system, especially in syphilitic meningitis of the base. Any of the cranial nerves may be affected, usually several of them. In fact, the inclusion of several nerves suggests at once a luetic origin, although the presence of a single gumma compressing a nerve at its point of emergence may limit the paralysis to that nerve alone.

The optic nerve is usually affected early in the course of basilar meningitis and the oculomotor is frequently attacked. The optic nerve may be affected by itself, that is, by gummata or Heubner's arteritis, but usually the involvement is secondary, either to gummous growths elsewhere, or to an infiltrating meningitis. A careful ophthalmoscopic and visual examination should be made. Ptosis may develop, first in one eye, then the other. If there is a great increase of intracranial pressure, we often see choked disc.

It is sometimes stated that paralysis of the eye muscles is pathognomonic of syphilis, but the best authorities do not put the case so strongly (Nonne, *et al*). The oculomotor is, however, frequently involved in syphilis and a careful test of all its muscles should be made.

Trigeminal involvement is manifest in areas of anesthesia on the face, variations of the pain sense, and disturbances of the corneal reflex. The peculiarity of this nerve, that is, the diffuse distribution of its muscles and branches, makes it extremely likely in a wide syphilitic process that some part of it will be

affected. A neuralgia, apparently having no connection with anything else, may appear, affecting say the first and second branches of the fifth, and be unsuccessfully attacked by coal tar products, electricity, injections, and so on; no history of syphilis is obtained perhaps in such a case, but vigorous antispecific therapy clears up the trouble magically.

The cranial nerves are not so commonly or so obviously involved, as a rule. Careful search may reveal that the eighth nerve is caught in the luetic process, although the patient himself seldom complains of symptoms pointing to this. The ninth, tenth, eleventh, and twelfth are sometimes diseased. Loss of the sense of smell points to inclusion of the first nerve; unfortunately the sense of smell is so seldom tested by the general practitioner. If this were done more frequently, it is probable that we should find the olfactory nerve more frequently affected.

Neuroses and Psychoses

The knowledge that syphilis of the central nervous system may give rise to various psychotic and neurotic symptoms dates back a long time. Leaving out of the question paresis (Scholtziuz, 1610, and Willis, 1672), the eighteenth century was fairly productive of observations concerning such conditions. Sanché, in 1777, described syphilitic mania, and amaurosis dates back thirty years before that. Bell described chronic mania in a syphilitic woman and Lagneau called attention to the fact that functional psychoses can occur in syphilitics. He divided them into melancholia, mania, dementia, and idiocy. Fournier described two varieties of syphilitic psychosis, a depressive state with dementia and delirious excitement. Heubner made extensive studies of the subject; he recognized a simple, or functional psychosis, and three forms of organic brain diseases. Probably the most valuable of the modern work along this line has been done by Plaut[67] who described 10 varieties of syphilitic psychosis; viz., simple luetic weakness of mind, syphilitic pseudoparesis, paranoid state with tabes, paranoid state without tabes, epileptic forms, short hallucinatory confused states, psychoses with syphilitic cardiac disease, psychoses resembling manic depressive, mental disorder due to syphilis as a psychic trauma and various grades of weak-

mindedness, psychopathic constitution, etc. Just what the frequency of occurrence of neuroses and psychoses in syphilitics is can hardly be said, but it is hardly possible for a syphilis of the central nervous system to make perceptible progress without causing mental symptoms of one sort or another. This is less to be wondered at when we consider the delicate and complex structure of the nervous system and reflect that apparently trifling psychical causes may stimulate extensive mental reactions. It is probably a good approximation to say that 5 per cent of all syphilitics show at one time or another psychotic or neurotic symptoms traceable to their lues.

Syphilis may cause psychic abnormalities in several ways. The actual fear of the disease may cause symptoms varying from a mild syphilophobia to severe anxiety depression. The nervous tissue itself may be injured by the postsyphilitic poison. Nutritional disturbances may be caused by a change in the blood itself, disease of the passages by which the blood is conveyed to the tissues or perhaps by long-continued mercurial treatment. These syphilitic neuroses and psychoses often show no distinctive pathology: the usual postsyphilitic picture is present, but nothing to indicate the reason for the psychic trauma. The nutritional changes in the blood are a diminution in the corpuscles and an increase in the albuminous constituents. Independently of the reduction in the red blood cells there is a diminution in the amount of hemoglobin. There is an increase in the white cells—a decrease in the polynuclear leucocytes and an increase in the mononuclear and transitional cells and eosinophiles.

The symptoms of the various forms of psychic disturbances associated with syphilis do not differ from their form when due to other causes. The key to the whole subject may be said to be this: The syphilitic virus injures profoundly the delicate and highly organized tissues of the brain. As a result of this trauma the brain reacts in a way characteristic of the individual and we have a psychotic or neurotic condition which might have arisen as the result of any other injury or stress. A few words may perhaps be said about the different varieties of disorder. Besides Plaut's classification we will touch upon neurasthenia and hysteria.

Syphilitic neurasthenia has been described by Kraepelin. A

neurasthenic-like state often precedes cerebrospinal lues or paresis and the diagnosis of neurasthenia has frequently been made in these disorders. A slight depression, insomnia, feeling of pressure about the head, irritability, fatigability, and so on, sometimes come on not long after the luetic infection.

Hysteria is a not uncommon concomitant of syphilis. Charcot states that the disease can give rise to hysterical symptoms just as toxins, such as lead, arsenic, and alcohol can. The cachexia due to prolonged mercurialization is sometimes accompanied by hysteria. Nonne points out that in order to attribute the hysteria to syphilis it is necessary that patients before their infection have never exhibited any symptoms of hysteria, also that the hysteria develop during the time of the syphilis and can either be improved or cured by antispecific treatment.

Taking Plaut's classification we have:

1. *Simple luetic weakness of mind.* This is usually due to a gross lesion of the brain which on the physical side causes a hemi- or monoplegia.

2. *Syphilitic pseudoparesis.* This is a difficult condition to diagnose, lying as it does midway between cerebrospinal syphilis and paresis and often having many of the characteristics of both. In general its symptoms may be said to be clinically those of paresis, but often with pronounced and persistent auditory hallucinations, negative Wassermann in the fluid in small quantities and a favorable reaction to antispecific therapy.

3. *Paranoid state with tabes.* These tabetics remain for years without deteriorating, but have delusions of persecution and often auditory hallucinations. I have a case, a man about fifty. His ataxia has been progressing gradually, but surely, until now, five years after the onset, he can hardly rise from his wheelchair; he believes, however, that he is getting steadily better. He is quite keen and clear mentally, but when placed in a hospital ward begins to develop paranoid ideas about those around him until, after a few months, it is necessary to move him to another ward. Here he is all right for a time and then the same sort of ideas are gradually formulated.

4. *Paranoid state without tabes.* This name is self-explanatory. These cases seem to be quite rare and resemble somewhat alcoholic paranoid conditions.

5. *Epileptic forms.* These develop convulsions as a result of the blocking-up of cortical vessels and are found very hard to distinguish from the so-called idiopathic epilepsy. They may show religiosity, hypocrisy, preconvulsive excitement or irritability, confused periods, dream state and other psychic phenomena usually associated with epilepsy.

6. *Short hallucinatory confused states.* These are also self-explanatory. They are transient and resemble the confused periods occurring in the epileptic forms.

7. *Psychoses with syphilitic cardiac disease.* Syphilis of the aorta is usually present in these. The symptoms vary. Irritability, apprehension, anxiety, depression, memory defects, etc., are present.

8. *Psychoses resembling manic depressive.* These resemble more or less closely the genuine manic depressive, but, on a more rigid scrutiny we find that the delusions are more grotesque than the same degree of excitement brings in the real manic: they may be entirely unrelated to the individual's usual manner of thought and he makes no effort at substantiation or argument as the maniac does. The neurologic signs usually point to the diagnosis, which is confirmed by the laboratory tests. These attacks may occur sporadically over years. A case of mine, a grocer of forty-five, developed an excitement which was diagnosed as manic and he was sent to an asylum. Here the lues was discovered and treated; the excitement gradually subsided and after about a year he returned and carried on his very successful business. About two years later a relapse occurred, but was cleared up in a few weeks under treatment. After being well for several years he died of an intercurrent disease.

9. *Mental disorder due to syphilis as psychic trauma.* This may take the form of syphilophobia—a fear of syphilis and its consequences—or it may result in a psychogenic depression, the form of which has no obvious relation to its cause.

10. *Various grades of weak-mindedness, psychopathic constitution, etc.* In these cases two factors are operative, poor heredity and syphilis. If a defective of any kind, imbecile, constitutional inferior, constitutional psychopath, and so on, acquire syphilis, we may get simply an exaggerated picture of his original weakness or we may have transient excitements, silly delusions, vague

and transient paranoid ideas. Or we may have lues that is congenital or acquired very soon after birth, retarding development, showing occasional convulsions, which are usually called epilepsy, and finally leading to serious defect.

The prognosis of luetic neuroses and psychoses is on the whole good. Of course when we have defective states, congenital or acquired, we can not hope for much, but the other psychic pictures may usually be caused to fade rather promptly by energetic antiluetic therapy. Of course the original mental make-up which caused the patient to show mental symptoms is still present and the symptoms themselves or others may reappear at any time.

The Relation Between Syphilis and Mental Disorder

The exact role of syphilis in the production of mental disorder has not yet been determined. Of course we know that paresis and cerebrospinal lues are due to syphilis and we are able to diagnose other psychoses as being caused in much the same way. But, besides this formidable total, psychiatrists are inclined to suspect this disease as playing a part in a great many other diseases. The Wassermann test is still too new in psychiatry to have admitted of the collection of statistics yet and even when these are available in large quantities there will have to be examination of them, formulation of theories, the discarding of some, and the retention of others, the testing-out of these latter and their verification or disproof by fresh statistics, and so on. In the large insane asylums of the United States there are many thousands of patients who have never had a Wassermann test. In most of these, however, this test is part of the routine admission procedures now, and the older patients are being examined from time to time.

White[68] says that alcohol and syphilis together are responsible for fully 20 per cent of insanity in males. Hough[69] in a study of the cases in the St. Elizabeth's Hospital in Washington, D. C., found that 10 per cent of the insanity in the institution was directly attributable to syphilis. During the year ending September 30, 1913, in New York State, 19.4 per cent of all male first admissions and 7 per cent of all female first admissions occurred on the basis of syphilis as an essential cause.

It is only necessary to pick up any asylum report and turn to the list of causes assigned to cases admitted during the year to see the high percentage of syphilis.

Serologic examination of imbeciles of all grades usually shows a high incidence of syphilis and there is also a growing suspicion that the disease may be connected in some way with dementia precox. This need not be, of course, a direct connection. It may be that the occurrence of syphilis somewhere in the ancestral strain has given rise to anomalies in the germ plasm which have resulted in the adult individual in definite structural and physiologic cerebral changes so that when he comes to the period of adolescence or meets with any great stress he reacts in a way incompatible with social requirements.

This whole subject is in its developmental period; what conclusions will ultimately be accepted can not be foretold with any degree of accuracy. The most we can say now is that from 20 per cent to 25 per cent of all mental disorder is undoubtedly due to syphilis and that very probably a great deal more of it, possibly another 20 or 25 per cent may indirectly be due to it.

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The following list of articles comprises some of the more recent important publications dealing with various phases of syphilis of the central nervous system.

General Articles

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CHAPTER XVIII

SYPHILIS OF THE EYE—ACQUIRED FORM

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Eyelids

Syphilis in any stage, from the primary sore to late gumma, may be met with in the eyelids. The frequency with which chancre occurs here varies greatly according to different authors, but it would seem, in searching the literature, to occupy the third place after the lips and fingers. The location is usually at the intermarginal space. The mode of transmission varies greatly; for we find in some cases kisses as the cause; in others the use of infected linen; in Russia the pernicious habit practiced amongst certain classes of licking the eyes; at times autoinfection.

Practically all authors agree that the most common form of primary sore at the beginning has much the same appearance as a chalazion or hordeolum. It is essentially indolent and developmental changes are slow, so much so that diagnosis is rendered rather difficult until eventually the characteristic indurated ulcer appears. However, it should be possible to subject serum from the ulcer to an examination under the dark-field thereby demonstrating the treponemata before the characteristic signs appear. As a rule, within two or three weeks after the initial lesion the lymphatic glands in the vicinity become involved, giving the evidence of commencing general infection, the submaxillary gland being involved, if the chancre is situated near the inner canthus, if near the outer canthus the preauricular gland, in accordance with the distribution of the lymphatic vessels of the lids.

The various syphilodermata are rare, though at times any one of them may occur, the usual site being at the folds and corner of the upper lid. Gummata are not uncommon, appearing in the late stage, generally located on the lid margin and, if superficial,

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breaking down to form characteristic ulcers. The necrotic process may be so extreme as to cause partial destruction of the lids. According to Hutchinson, Jr., gummata of the lids are found in women more frequently than in men, and the upper lid more often than the lower.

The Tarsus

The tarsus is liable to syphilitic infection in the late stages, either in the form of circumscribed nodes, or a diffuse gummous infiltration, in which condition the lids become so thick that it is impossible to evert them. This condition shows little tendency to break down. If incised it shows no tendency to bleed and presents a lardaceous condition. The disease runs a long chronic course.

Conjunctiva

Primary lesions occur rarely, the relatively most frequent seat being the conjunctiva of the lower lid and transition fold. The lesion presents a lardaceous swelling of the conjunctiva, with slight irritation and edema associated with profuse mucopurulent secretion.

A few cases have been reported of chancre of the bulbar conjunctiva, in which the lesion closely resembled, at first, a phlyctena. In the late stages papules, either single or multiple, have been described. They show small tendency to break down and disappear under antisyphilitic treatment. As a rule gummata create more or less irritation as they involve the underlying structures. De Schweinitz calls attention to a particular type of conjunctival inflammation occurring in subjects of pronounced syphilis (conjunctivitis syphilitica) in the form of granulations similar to trachoma follicles. This condition does not respond to local treatment, but does to antisyphilitic treatment.

Sclera

Gummata of the sclera, *per se,* are of such rarity that most of the text books devote little attention to a description of them. I have seen one case in a colored male, age about forty years, the gumma appearing as an almond-shaped tumor, projecting

from the sclera midway between the limbus and equator. The color was a dark cherry red, a zone of scleritis extending around the tumor, the scleral and conjunctival vessels greatly engorged and congested and the entire conjunctiva more or less edematous. The tumor was immovable and slightly sensitive to touch, lacrimation was profuse. The ciliary body, cornea, and iris were clinically not involved. The ophthalmoscopic examination was negative; Wassermann reaction, triple plus. Heavy doses of potassium iodide and inunctions of mercury caused the tumor to gradually disappear, leaving a faint trace in the thinning of the sclera.

The gumma may spread to the ciliary body, producing a cyclitis and if situated near the cornea it may also become involved. If untreated, the gumma may ulcerate, causing perforation and loss of the eye.

Lacrimal System

With the literature at hand, it has been impossible to find any true syphilitic lesions of the lacrimal gland, although de Schweinitz and Duane both call attention to an induration or gummatous infiltration, and Weeks quotes a case of primary lesion recorded by Anagarsa.

Nasal Duct

Stricture of the nasal duct may occur as a consequence of luetic periostitis of the lacrimal canal, or extension from the nasal cavity. This causes an obstruction to the flow of fluid through the duct. The lacrimal sac soon becomes distended and the retained secretions become septic. By exerting pressure over the sac, pus can be pushed through the puncta into the conjunctival sac where it becomes a never ending source of danger, for the slightest corneal abrasion may thereby become infected, leading to destruction of the eye.

Cornea

Acquired syphilis seldom attacks the cornea; however, certain pathologic changes do occur, whose etiologic factor can be traced to the acquired form. Keratitis punctata syphilitica described by de Schweinitz, Mauthner, Fuchs and Hock appears in the later stages of the disease, and is characterized by the presence

of minute circumscribed grayish white spots in the parenchyma of the cornea, usually confined to the center. These spots generally disappear without leaving any trace. The condition is unaccompanied as a rule by iritis or any circumcorneal injection.

Deep Vascular Keratitis

Deep vascular keratitis, though occurring in both forms of lues, is probably met with more frequently in the acquired form. It appears as a pale red patch occupying a small portion of the circumference of the cornea, rarely over one quarter and seldom covering the pupillary area. Examination under the corneal loupe discloses minute blood vessels, beginning at the corneal margin and extending into the deep layers of the substantia propria, which is more or less cloudy for a distance around the vessels. It is accompanied by symptoms of irritation, photophobia and disturbance of vision. The condition is of a more or less chronic duration, the cornea finally becoming transparent again. (Weeks.)

Neuroparalytic Keratitis

Neuroparalytic keratitis is generally conceded to be due to atrophic disturbance of the trigeminus, consequently this condition can be at times traced to syphilitic deposits, along the course of the nerve. In this form of keratitis, a grayish infiltration of the cornea first takes place in the center which generally spreads until the entire cornea may become involved with the exception of a narrow margin around limbus, which usually remains free. Sloughing generally follows with the loss of the entire cornea. A striking fact is that the eye shows practically no irritation, ciliary injection is present, there is no lacrimation and the patient does not complain of pain. When tested the cornea is found to be insensitive.

Gumma of the cornea has been reported, but is exceedingly rare. In a case reported by Terson, there was a grayish yellow localized infiltration of the cornea accompanied by violent iritis. Luetic treatment was given with the result that the infiltration disappeared leaving a dense scar.

Lens

It is extremely doubtful whether syphilis ever directly affects this structure, it being of epiblastic origin. Following any inflammation of the ciliary body, the nutrition of the lens is liable to be interfered with, in which case it is apt to become opaque. For this reason, individuals affected with syphilis are more prone to cataract than those unaffected with the disease.

The eyes affected with cataract should be examined carefully for any sign of lues, for these cases are apt to be complicated with choroiditis in which case the prognosis as to restoration of useful working vision should be guarded.

Uveal Tract

Bearing in mind the anatomic, physiologic and pathologic continuity of the different portions of the uveal tract, it seems scarcely conceivable that an inflammatory condition can be strictly limited to a single part; nor is this so; but for convenience sake we speak of that particular part as being inflamed, when certain specific signs and symptoms present themselves which clinically point to that part as the one most involved. Being of mesoblastic origin and taking into consideration the well-known fact that syphilis exhibits a peculiar affinity for attacking connective tissue elements, it is small wonder that syphilis enters so largely as an etiologic factor in all inflammatory processes of this particular structure of the eye.

Iris

As early as five or six weeks after the initial lesion, the roseola syphilitica has been observed in the iris, and in some cases even before the appearance of the cutaneous eruption (Roemer). Clinically localized hyperemias are seen in the center of the iris, which portion is abundantly supplied with minute vessels, and are supposed to be due to capillary emboli of treponemata. How often this condition occurs is difficult to ascertain, owing to the fact that it causes no trouble in the iris and quickly disappears.

Almost any grave disease may cause inflammation of the iris,

but according to different authorities, syphilis has been found to be the etiologic factor in from 40 to 70 per cent of all cases, whereas the percentage of cases of syphilis which acquire iritis during the course of the disease varies from .42 to 5.37 per cent (de Schweinitz). Hence, it is seen how vitally important it becomes to ascertain at the earliest possible moment the etiology of any case of iritis, especially so as all ophthalmologists admit that frequently it is impossible to differentiate syphilitic iritis from iritis arising from other causes.

Iritis in all its forms, from whatsoever cause, presents certain conditions in common; viz., pericorneal injection, due to injection of the anterior ciliary vessels producing the characteristic deep pink color. In conjunction with this the conjunctival vessels are always engorged, turbidity of the aqueous due to exudate, blood or pus. Change of color in the iris is pronounced, due to the congestion and swelling whereby the iris pattern is obliterated, producing the well-known "muddy iris." The pupil is contracted, due, in part, to hyperemia and in part to irritation of the peripheral nerve filaments. Formation of posterior synechia or attachments between the anterior capsule of the lens, and the iris vary in size, number and firmness. The iris may be bound down throughout the entire pupillary margin by the inflammatory process. These inflammatory bands are easily demonstrable by the instillation of atropine, giving the characteristic irregular pupil of iritis. The pain is severe, throbbing in character, not confined to the eye itself, but extending to the temple and down the side of the nose and at times extends even to the teeth. The vision is disturbed in proportion to the amount of cloudiness which occurs in the media.

In cases of iritis where there is involvement of the ciliary body, the cornea under oblique illumination is found to be hazy and upon close examination, deposits are seen on Descemet's membrane scattered over a triangular area of the lower portion of the cornea. The deposits are leucocytes, which are deposited by the aqueous humor upon the back of the cornea and remain there. They may contain pigment granules, showing their origin from the uveal tract (Parsons).

It is stated by Friedenwald that in all cases of iritis, the

cornea is affected either by infiltrations into the substantia propria or with deposits on Descemet's membrane. The former are occasionally in evidence, the latter always.

Roemer divides all forms of iritis into two large groups; those in which the anterior surface of the iris is the part particularly affected, and those in which the deeper layers are affected. He likewise states that the etiologic factors which produce inflammation of the deeper layers are mainly syphilis and tuberculosis. However, as the differentiation can not be made save with the aid of a Zeiss loupe and even then the two conditions undoubtedly blend to such an extent that this test as a diagnostic point, can not be relied upon. Hence, in cases where the physical examination and history do not conclusively point to the cause, it is necessary to resort to the serum diagnosis. In fact all cases, in my opinion, should be subjected to this most valuable test.

Syphilitic iritis usually makes its appearance in the form of plastic iritis in the early stages of the general affection, usually between the second and ninth month, although it may be delayed until the second year. Both eyes are usually affected, though not always simultaneously. It is generally acute, and after a cure does not have the same tendency to recur as the iritis following rheumatism or gonorrhea.

Iritis Papulosa or True Syphilitic Iritis

In the form of syphilitic iritis described in the preceding paragraphs etiologic diagnosis could be made only after a thorough physical and biological examination of the patient. This is not the case in iritis papulosa; here the eye presents certain well-defined clinical signs which immediately suggest lues to the examiner.

There is a high degree of injection of both conjunctival and ciliary vessels. The iris is discolored and its pattern obscured to a moderate degree. Examination with oblique illumination reveals the pressure of nodules situated usually at the pupillary border of the iris, although they are occasionally seen near the ciliary border or even in the tissue between. They present a yellowish red or brown color and are about the size of the

head of a pin. These nodules project into the anterior chamber or pupillary space. Focal illumination also brings out posterior synechia.

Microscopic studies bring out the fact that there is no sharp line of demarcation between specific plastic iritis and iritis papulosa, as it has been demonstrated microscopically that there are nodules present in all cases of plastic iritis which clinically give no sign, being too minute to be observed.

Gumma

This condition occurs in the late stages of the disease and is of greater rarity than the papule. It is usually a solitary tumor of considerable size and appears almost always at the ciliary margin of the iris; is usually seen in only one eye. The iris is more or less involved as is the ciliary body. It may undergo degeneration or may proliferate and fill the anterior chamber or it may perforate the sclera by extension through the ciliary body.

Examination of the cornea in the vicinity of the tumor will generally show a slight haziness and the formation of deposits in Descemet's membrane. In case of recovery a scar is left in the shape of atrophy of the iris fibers at the site of the tumor.

Ciliary Body

Inflammations restricted to the ciliary body alone are exceedingly uncommon, owing to the intimate anatomic relationship between this structure and the rest of the uveal tract. Syphilitic cyclitis is essentially an iridocyclitis of the plastic type. The disease is acute, both eyes being affected, though not always simultaneously.

The symptoms leading to a diagnosis are the following: circumcorneal injection, neuralgic pains radiating from the eye through the head, extreme tenderness upon pressure over ciliary region; turbidity of the aqueous, posterior synechia binding the iris to the anterior capsule of the lens; a deepening of the anterior chamber; exudate or blood in the anterior chamber; opacities in the anterior layers of the vitreous, and deposits of exudation on the posterior layer of the cornea.

Fig. 123.—Iritis papulosa.

The tension is high or low according to the character of the inflammation. In severe cases the choroid, retina and optic nerve may be involved.

Gumma is of rare occurrence. It is usually monocular, is of relatively rapid development, and the iris is more or less involved. The condition is accompanied by neuralgic pain. Brixa reports a gumma accompanied with extensive syphilitic changes in other parts of the eye.

Choroid

Next to iritis, choroiditis is the most common luetic manifestation in the eye. The disease assumes the exudative form, and, whereas it is generally disseminated in character, yet it may be diffuse, circumscribed or central, hence it is not safe to attempt to make a diagnosis of syphilis by the appearance of any one particular form of choroiditis.

It occurs usually in the early stages of the disease, anywhere from the fourth month to the second year, although it may not appear until later. Both eyes are usually affected, and the disease runs a chronic course, lasting over a period of six weeks to three months or more. If seen in the early stages, the ophthalmoscope reveals the recent foci of inflammation as well-defined yellowish or grayish spots scattered throughout the fundus; occasionally retinal vessels can be seen to pass over them. These spots are due to infiltration of the choroid. The overlying retina is slightly cloudy and edematous. Small diffuse opacities are seen in the vitreous, usually in the posterior portion, owing to the exudate having passed through the retina. In the later stages the exudate in the choroid becomes organized, forming fibrous tissue which more or less destroys the normal structure of the choroid and overlying retina, so that the color of the spots gradually changes to white, due to the atrophy of the choroid and retina, whereby the sclera is seen to shine through. In the last stages, masses of pigment are seen heaped around the edges of the atrophic areas.

The symptom which first attracts the patient's attention is the diminution of vision. If peripheral, vision is very little affected, while if the macula is involved, there is a great diminution. There is a distortion of objects (metamorphopsia),

straight lines being bent in various directions, occasionally objects appear smaller than normal, (micropsia); or at times larger (macropsia). This is undoubtedly due to the displacement of the rods and cones as the exudate in the choroid raises up the retina slightly. The prognosis should be guarded owing to the fact that there may be an extension of the disease to the retina and optic nerve, or forward to the ciliary body and choroid.

Retina

Syphilis may manifest itself in any one of the various forms of retinitis, but, as a rule, it is either circumscribed or diffuse. In the former it makes its appearance near the disc, in the shape of a cloudy swelling which radiates along the course of the vessels; vitreous opacities are present. The nerve head is cloudy, of a yellowish red color, the edges are indistinct, the arteries are practically normal, while the color of the veins is darker; there is exudation along the lines of the vessels (perivasculitis). In the latter form the entire retina is edematous and grayish in color, and throughout the retina, and especially near the macula, grayish spots are present.

In syphilitic retinitis, hemorrhages into the retina are rare, though they may occur. The disease generally occurs in from one to two years after the infection, one eye may be affected, but as a rule both eyes are usually involved, but not simultaneously. About 8 per cent of luetics develop retinitis (Alexander). Whereas iritis is rare in other forms of retinitis, it is by no means uncommon in the specific varieties, and likewise iridocyclitis is apt to occur.

The subjective symptoms are defective central vision, marked in the late stages, decrease in visual acuity under weak illumination, distortion of objects (metamorphopsia), irregular and concentric contraction of the peripheral field, positive scotomas in the central field. Although the onset is sudden the disease invariably follows a chronic course.

The prognosis depends upon the early beginning of appropriate treatment, and even then the condition may lead to one of total atrophy of the nerve. Syphilitic retinitis often leads to an extensive involvement of the choroid, to which condition,

the term choroidoretinitis is applied. A great many authors consider this as in reality beginning in the choroid due to the extensive changes which occur in that structure, and the comparatively slight involvement in the retina, while, on the other hand, other authors consider it as purely a retinal disturbance, usually in the outer layers.

The ophthalmoscopic signs are: dustlike opacities in the posterior portion of the vitreous, cloudiness of the retina around the disc, which is more or less hyperemic, perivasculitis of the retina and choroidal vessels, numerous isolated yellowish or white spots of exudation beneath the retinal vessels throughout the choroid which follow the same course as in disseminated choroiditis, ending in atrophy.

The subjective symptoms are: vision diminished, flashes of light, night blindness, metamorphopsia, scotomata and contraction of the visual field.

A rare and peculiar form of retinitis, which may occur in syphilis was first described by von Graefe, and is that form of retinitis known as central relapsing retinitis. It occurs in the late stages of the disease and is marked by a sudden diminution of central vision which may last for a few days, when the vision is practically restored only to be followed by a relapse. The prominent symptom is a central scotoma of which the patient complains.

The ophthalmoscope reveals a yellowish or grayish cloudiness in the macula, which may entirely disappear after the first few attacks, but as the disease progresses, the changes in the macula and the choroid become pronounced.

Retinitis pigmentosa and retinitis proliferans, at times, have as their etiologic factor, syphilis.

Optic Nerve

This structure may be affected throughout its entire course, or any part of it may be the seat of the inflammatory process. The intracranial portion, according to Uhthoff (quoted by Parsons) is affected most commonly, for here it may be attacked by gumma, or by extension of gummous infiltration from the

meninges, for the neighborhood of the chiasm is a favorite spot for gummous meningitis.

With the statistics at hand, syphilis seems to stand forth as to etiologic factors. Here, as in inflammatory conditions, a differential diagnosis can not be absolutely made by the ophthalmoscopic picture, although several writers bring out the fact that in papillitis of syphilitic origin there is very characteristic thickening of the retinal vessel walls. White striæ, which are the result of the inflammatory process accompany the vessels out into the retina.

Papillitis

Papillitis, or inflammation of the intraocular portion of the nerve, manifests itself externally by no sign except that the pupils are dilated in proportion to the diminution or absolute loss of vision. The ophthalmoscope reveals the following picture: increased redness of the disc, the margin becoming indistinct owing to the swelling of the disc, which gradually shades off into the surrounding retina. The retinal vessels are altered; the arteries are smaller than normal, and may or may not be tortuous. The veins are dark, distended and tortuous, especially so when they dip down from the swollen papilla into the retina. Hemorrhages are of frequent occurrence, situated on the nerve head, or in the surrounding retina and generally of a fan shaped character. The vision may or may not be affected.

The peripheral fields of vision may be affected or else there may be irregular or concentric contraction. The blind spot becomes larger as the swelling of the disc increases.

Choked Disc

Although tumors of the brain are by far the most frequent cause of this condition, yet syphilis can not be disregarded. The disc is immensely swollen, protruding out into the vitreous like a mushroom, the color is of a glossy grayish red. The arteries are small, while the veins are immensely distended and tortuous, resembling a bunch of angle worms. Occasionally hemorrhages are seen in the disc. The surrounding retina ap-

pears normal. The swelling of the disc is primarily due to edema.

Gumma at the base of the brain may be the cause of the choked disc in either one or both eyes.

Retrobulbar Neuritis

Externally the eye shows no symptoms, save the dilation of the pupil, which is in proportion to the defect of vision. The patient complains of central scotoma, and usually there is pain upon movements of the eyeball. The ophthalmoscope first reveals nothing pathognomonic, but in the later stages there is hyperemia of the disc, the arteries appear small, while the veins are engorged. The condition is one of interstitial neuritis, which is apparently located in the intraorbital portion of the nerve.

Atrophy of the Optic Nerve

Atrophy of the optic nerve may be primary or secondary. Any of the above-mentioned inflammations of the optic nerve may naturally have as their termination atrophy, consequent upon the changes produced in the nerve by the inflammation, as primary atrophy is a symptom produced by certain diseases of the nerve itself.

In from 40 to 50 per cent of cases of progressive primary atrophy, tabes is the etiologic factor, hence it behooves us to investigate for other symptoms of this disease. The ophthalmoscopic signs are: a bluish white appearance of the papilla, the lamina cribrosa is visible, the margins of the disc are sharply defined. The excavation which is shallow extends to the margin of the disc. Both veins and nerves are smaller than normal. The patient complains of a gradual decrease in vision. The fields of vision for colors are first affected in the following relations: green, red, blue and white. As the peripheral fields contract the central vision fails until finally total loss of vision ensues.

Ocular Muscles

Syphilis is by far the most frequent cause of paralysis of both the extraocular and intraocular muscles and, now that the etiology of tabes has been definitely established by Noguchi,

it is safe to estimate that it is the etiologic factor in at least 75 per cent of all cases.

Irrespective of the cause, paralysis of the extraocular muscles presents certain characteristic symptoms which are practically present in all cases, viz., diplopia (double vision), owing to the images for both eyes from an object falling on dissimilar points of the two retinas, and, therefore, projected to different parts of the field; vertigo, owing to diplopia and defective orientation; limited motion of the eyeball in the direction of the action of the affected muscle; tilting of the head in order to correct as far as possible the diplopia; false orientation, whereby the patient is not able to locate objects in their true place with the paralyzed eye.

The seat of the lesion producing ocular paralysis may be cortical, nuclear, fascicular basal or orbital.

Lesions of the cortex with the exception of ptosis (Duane), never cause paralysis of individual muscles, conjugate paralysis being the result of such lesions. Lesions on the floor of the fourth ventricle, produce, as a rule, paralysis of several muscles, and generally it is bilateral. Fascicular lesions, as a rule, cause oculomotor paralysis of the same side with paralysis of the extremities of the opposite side. Basilar lesions, as a rule, affect various nerves in succession as those supplying the ocular muscles, the facial, the olfactory, the trigeminus, the optic nerve, etc. In orbital lesions, the muscles and nerves are usually affected mechanically and are diagnosticated by symptoms indicative of affection within the orbit, such as pain produced by pressure on the eyeball, protrusion of eyeball, monocular optic neuritis, etc.

Paralysis of the intraocular muscles is of frequent occurrence in syphilis and, as a rule, it is unilateral although it may be bilateral.

Argyll Robertson Pupil is that condition in which we find that the pupil fails to contract to light, but does to convergence and accommodation. It is quite frequent in tabes. Usually it is bilateral, but it may be unilateral.

With regard to the seat of the lesion, de Schweinitz says, "It has been placed in the fibers which pass through from the proximal end of the optic nerve to the oculomotor nuclei by

some authors, and by others it is considered to be nuclear."

Ocular palsies may make their appearance in the early stages of the disease, cases having been reported as early as the fifth or sixth month, however, they are more frequent in the later stages, especially is this so of the intraocular muscles. Statistics show that the third nerve is the one most frequently involved in syphilis. It may be partially or completely affected. A complete paralysis is easily recognized. There is complete ptosis of the upper eyelid and the patient is unable to move the globe except outward and downward, this movement being due to the noninvolvement of the sixth and fourth nerve. The pupil is dilated and does not react either to accommodation or light. Diplopia is present.

Treatment

All cases of syphilitic involvement of the eye should be under intensive general treatment in connection with whatsoever local treatment each particular inflammation demands. Only the local will be touched upon in the following paragraph.

Nasal Duct.—If stricture is suspected, the punctum should be dilated sufficiently to allow the entrance of the lacrimal syringe, and water should be forced into the nose. If this is not possible, the duct should be probed. If this can be done easily, in all probability no other treatment will be necessary. However, if bony obstruction protects the passage of the probe, it is far wiser to remove the sac than to subject the patient to the wearing of a style, permanently, which necessitates the splitting of the canaliculus and the opening of the occluded nasal canal.

Keratitis.—In keratitis it is important to keep the iris well dilated to prevent synechia from forming. Atropia 1 per cent should be used every two hours, hot applications every two hours, and the eyes should be protected from light by the use of dark glasses. In the late stages of keratitis, dionin is of aid in clearing opacities.

Iritis.—By far the most important drug for local treatment is atropine, 1 per cent of which combined with 1 per cent of cocaine should be instilled in the eye every two hours. This

treatment should be continued until all ciliary congestion disappears. In order to alleviate as much as possible the dryness of the tract produced by atropine, it is well to compress the tear duct after instilling the drug. Pain is relieved by hot applications, preferably moist, applied with some soft material. Leeches should be applied to the temple thereby reducing the congestion and aiding the action of the atropia. In some cases dionin in weak solution is exceedingly grateful.

Iridocyclitis.—Naturally the same treatment used in iritis should be immediately instituted in case of iridocyclitis, attention being paid especially to the tension, which in inflammation of the ciliary body is liable to be increased. However, the atropia should be used, as the quicker the iritic involvement is got under control, the quicker the tension becomes normal. In cases of excessively high tension, paracentesis of the anterior chamber can be done. It is seldom that the increase of tension in these eyes leaves any permanent damage.

Choroiditis.—All use of the eyes should be prohibited and the eyes should be protected from all bright light by the use of dark glasses. The iris should be kept under inspection and proper treatment instituted in case of extension of the inflammatory process.

Retinitis and Optic Nerve

Retina and Optic Nerve.—Protection of the eyes from light and absolute rest from all use.

Intentionally, no mention was made of the use of arsphenamine in ocular affections in the previous paragraphs, as it was thought best to briefly outline some of the more recent opinions brought forward by various ophthalmologists.

When arsphenamine was first introduced to the medical profession, ophthalmologists, realizing that it was an arsenical preparation, were loath to begin the administration. In reported cases of syphilis of lids it has acted promptly. The best results so far, according to literature, seem to be found in inflammation of the uveal tract, especially in the cases of nodular iritis, several cases having been reported in which a definite cure was affected in a few days.

Choroidal lesions have also cleared up rapidly under its administration.

In cases of the involvement of the retina and the nerve, there is a great diversity of opinion regarding its use. Many cases are on record where optic neuritis and neuroretinitis have followed its use, especially when the case is complicated by retinal hemorrhages. Dolganoff, however, states that arsphenamine has no deleterious effect on the nervous elements of the eye, while various others claim that ocular inflammations following its use are to be looked upon as further evidence of lues and the treatment should be intensified, combined with mercury and potassium iodide.

In the ocular palsies, opinion is also divided, yet it appears from case reports that, if the treatment is begun early, satisfactory results are obtained.

Where most was expected of it, arsphenamine has singularly failed, namely, in interstitial keratitis. Many explanations have been brought forward, but, so far, none are satisfactory. In nearly all cases where it has been used, the second eye had become involved, hence, it does not seem to even have a prophylactic effect. Lamb advocates the subconjunctival injection of salvarsanized serum (Swift-Ellis method) and reports satisfactory results in many cases of iritis, chorioretinitis and involvement of the nerve.

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CHAPTER XIX

SYPHILIS OF THE EAR

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While it has long been recognized that syphilitic disease attacks every division of the auditory tract, from the auricle to the ultimate nuclei, the frequency with which this region is invaded is a point of great disagreement among observers. There are several reasons for this, but the chief one is, perhaps, that from the nature of the disease a primary lesion is not to be expected here, and hence is not recognized when it does occur. However, it may be stated definitely that, on the whole, primary syphilitic affections of the external ear are very rare.

Thus, in the entire literature touching on this especial subject, I have been able to find only 32 cases, of which at least 25 were "innocent" infections, such as those due to contact with an infected towel, the bite of an antagonist, etc. On the other hand, as a secondary manifestation, syphilis of the external ear is not uncommon, as the auricle and canal share the cutaneous invasion, especially in those cases where the face and scalp are involved. The skin lesions may be macular, papular or pustular; in fact, the pustular form is at times indistinguishable from this usually characteristic sign of variola. I once saw this mistake made, though it was one easily explained, as there was an epidemic of smallpox in the neighborhood. While gummata are rare in this region they yield readily to constitutional treatment, but, when treatment is long delayed, are very destructive to the cartilage and leave deep, contracted scars (Buck, Hessler, Field, Politzer, West).

A primary sore of the meatus itself is most uncommon, for obvious reasons and Sendriak reports the only two cases that are contained in the literature, in his review of it. The immunity from condylomata enjoyed by the pinna is not shared by the meatus, as here they are found rather commonly, though nearly always easy of diagnosis, as they appear chiefly as

complications of other syphilitic lesions in the body. The initial stage of infiltration and redness may easily escape notice, but as soon as the inflammation strikes into the cartilage, intense pain ensues, radiating over the side of the head, frequently accompanied by tinnitus and deafness. These grayish red, ragged, warty excrescences may heal by resolution or terminate in unhealthy, confluent ulcerations associated with an offensive purulent discharge. These ulcers are very resistant to treatment, requiring several weeks to several months to heal under constitutional treatment, which usually suffices as a therapeutic measure. Cicatrices may or may not result, though in their absence, there is permanent destruction of the hair follicles and secretory apparatus. Most observers agree that atresia of the canal generally does not occur, though I have twice seen this unfortunate result from neglect of treatment and failure to report for observation until the process had become deep-seated. It must, however, always be regarded as one of the possible complications, and proper precautions taken to prevent it. Local cleansing must be rigidly carried out, such as preliminary wiping with peroxide, drying and keeping in constant contact with yellow oxide of mercury or black wash. Frequent cauterization with lunar caustic or chromic acid will hasten healing.

Ulcerations of gummous origin situated on the external ear are rare and occur seldom, if ever, in the absence of tertiary lesions elsewhere in the body. Indeed, the diagnosis rests almost solely on this corroborative evidence and on the effect of specific treatment, as they are lacking in such characteristics as would warrant a definite diagnosis without further signs. Instances are not common in the literature, but where found the lesions are usually described as having flattened bases with steep, elevated margins, sharply demarked from the surrounding parts. Specific treatment combined with local cleansing and dusting with mercurial powders generally establishes a firmly healed site, though cauterization at times is indicated when the lesion appears sluggish. Were the drum exposed to easy inspection, its involvement would probably be noted more frequently in printed reports. This fact, together with the additional one, that syphilis is generally treated by

an attendant not gifted in examination of the ear, or especially interested in its behavior, perhaps accounts for the paucity of reported cases. However, it is well to remember that the canal is frequently occluded by the same process that may be causing the drum lesion, thus effectually preventing such inspection as the examiner might be eager to make. I find but three cases recorded (Lang, Baratoux, Ravogli).

Syphilitic Infection of the Eustachian Tube and Middle Ear

The reports of the past twenty-five years so seldom mention syphilitic infection of the tube as a primary lesion that it seems hardly necessary to dwell on this complication, though in the early reports this infection, chiefly through the use of an infected catheter, was accomplished oftener than it is pleasant to contemplate. Despite the casual mention of Politzer and Dalby, who record its rare occurrence, West considers that there have been more cases than the very considerable number actually reported. This speaks eloquently of the lack of ordinary cleanliness (much less of actual asepsis) and of careful, gentle catheterization, since mere contact would not usually cause infection. West has gathered reports of ninety-five cases, as published by Burow, Sendriak and Lancereaux, the last of whom is not certain of the specific nature of the cases he reports.

As might be supposed from a knowledge of the histology of the part and the all-pervading nature of the syphilitic poison, infection of the middle ear occurs in all degrees and in all stages of the disease, in which an extension through the tube is the most easily understood means when such a tubal lesion exists. Where this causes a catarrhal swelling and tumefaction of the tube, the clinical picture in the middle ear is no different from that of a simple infection, such as retraction of the drum, which is congested, reduced hearing, and possibly a negative Rinné. In early syphilis one of the most constant signs is reduced bone conduction, but this is so important a point that it will be discussed at length later on. It can be stated positively that there is no characteristic appearance of the drum, or any definite clinical aspect in a case under the foregoing circumstances. If inflation does not give immediate relief, then we

have to deal with something beyond the middle ear; infection of the labyrinth, with or without syphilis of the central nervous system. While it is not susceptible of proof, and is somewhat a matter of academic interest, it seems reasonable to suppose that the mucosa of the tympanum is subject to the eruptive conditions found elsewhere in the secondary stage. Here the infection may be catarrhal, adhesive catarrhal or suppurative (Politzer), but, again, there is no typical picture to justify the diagnosis of syphilitic origin, as this can be established only after the rapid destruction of the membrana tympani and the marked shortening of the bone conduction. The occurrence of a simple suppurative otitis media complicating a syphilitic infection is not infrequent, but the course of the suppuration is relatively so much less malignant and the effect of specific treatment is so little evident in the ear condition that the differential diagnosis soon becomes apparent. The appearance of tinnitus, vertigo and severe loss of hearing should suggest a deeper invasion than that of the middle ear, though both may coexist. All the foregoing conditions are readily submissive to energetic, early treatment in most cases, but when delay has allowed destruction of the drum, entirely or in part, ossicles or any part of the tympanic walls the prognosis is bad; in fact Bell's palsy is one of the likely results.

The responsibility of tertiary syphilis for any suppuration in the middle ear is even more difficult to establish than that of the secondary period, yet when it does occur the destructive changes are rapid and extensive. The ravages of an untreated tertiary syphilis when once established in a bony nidus would lead one to the natural expectation that a brain abscess would complicate a suppurative middle ear condition where the tympanic walls were necrosed and even the petrous portion of the temporal bone eroded, yet such is rarely the case. Baumann's case, for example, went to operation for mastoid abscess, there being polypi and small sequestra in the middle ear, but the wound remained open until potassium iodide was administered, yet no brain complication was seen. While invasion of the cranial cavity is not usual, yet erosion of the wall of the lateral sinus and of the carotid artery has occurred with great loss of blood (Hessler). Pollak was the first to describe gummata of the

mastoid process, which occur at times independently of any aural symptoms (Pollak, Collet, and Beuten). West reports four cases in which there was no history of syphilis, but the administration of specific treatment quickly caused a disappearance of the mass and established its nature. This latter point was totally obscure, and three of the cases were in many ways anomalous.

Syphilis of the Internal Ear

Auditory disturbances of syphilitic origin usually appear in the late secondary or early tertiary period, though Politzer reports two cases which show the wide range within which hearing may be affected after exposure. The first had distinct acoustic symptoms seven days after the appearance of the chancre, and the other had no symptoms till the lapse of twenty-one years, when a gumma of the head appeared. Again, disturbances in the hearing function may appear without any other syphilitic manifestation whatever. Nowhere does syphilis show its protean, elusive, unexpected and confounding characteristics more than in its insidious attack on the internal ear. This condition of baffling obscurity, its dire effect on the hearing of the patient with all that this loss spells in social and economic disaster combine to render this division of aural syphilis the most absorbing to the investigator, and the most important to him and to humanity.

Owing to the insidious nature of the infection and to the usually somewhat casual nature of the aural examination (if, indeed, any be made at all), this complication, as before remarked, has escaped record very often; so the frequency with which auditory disturbances complicate constitutional syphilis can not be estimated with any satisfactory degree of accuracy. Thus, Politzer accepts the vague statement that from 7 to 48 per cent show aural lesions (Schwabach, Kretschmann, Wiese), which, in justice to him, is the view generally held, though it is hardly better than no estimate at all. With West, I believe that 5 per cent is sufficiently near the proper proportion to serve as a guide in study and investigation. Certainly 48 per cent is much too high a percentage in America. Whatever the true estimate may be, the wide difference of opinion shown by the figures 5 and 48 is an evidence of the unsatisfactory condition of the history and

records of such cases. There is another aspect of these cases which offers a more easily ascertained incidence, for it seems nearly certain that about 50 per cent of all aural lesions that do occur in aural syphilis make themselves manifest in the secondary period, and accordingly they should be searched for in this stage.

The early writers were almost a unit in their conviction that the labyrinth was the part affected in syphilitic disease of the internal ear, and Habermann and Kreibich wrote so convincingly, and the weight of their influence was so great that this belief was well-nigh universal for a while. However, of those to dissent, Gradenigo was the first to attempt any systematic differential diagnosis, and rather leaned to the belief that the lesion was oftener one of the nerve trunk, though he admits that a clinical differentiation presents one of the most difficult of problems. On the other hand, Rosenstein makes the rather oracular statement that only rarely is the lesion labyrinthine, but Nonne puts his finger on one of the most significant and important facts, hitherto unknown or regarded as negligible, when he comments on the coincidence that frequently disturbances of the acoustic nerve are associated with similar disturbances of other cranial nerves. This observation paves the way to the recognition of the revolutionizing nature of the statement of Swift and Ellis, who have shown rather convincingly that sudden deafness in the presence of syphilis is rarely due to any infection of the eighth nerve, or labyrinth, alone, but is generally a manifestation of that very serious disease, syphilis of the central nervous system, of which more will be said later. In his review of the literature, Benario seems to prove that the eighth nerve is oftener affected in early syphilis than any other cranial nerve (Habermann, Mayer, Rigaud, Politzer, Rozier). Nonne further observes that in his opinion the involvement of the eighth nerve is associated with a basal meningitis, a fact that is emphasized by Swift and Ellis, though they state the matter somewhat differently, adding that this is demonstrable by lumbar puncture. Knick and Zaloziecki are credited with precedence (1911) in their demonstration of a definite change in the spinal fluid in the presence of syphilitic disease of the eighth nerve. This change, viewed in the light of the symptoms, seems to establish the clin-

ical fact that in the early cases of auditory disturbances, and perhaps the late as well, such disturbances are due to an involvement of the eighth nerve in the course of a syphilitic meningitis.

Glogau, observing that many cases of tabes dorsalis showed impaired hearing, made careful tests and found that from 40 to 50 per cent were suffering from impaired or complete loss of hearing in one or even both ears, and also shortened or complete loss of bone conduction. Swift and Ellis urge that sudden deafness of the syphilitic be regarded not merely as isolated disease of the eighth nerve or labyrinth, but as an incident in the course of syphilitic disease of the central nervous system. The prognosis of syphilitic deafness, notoriously bad, has been greatly improved by their method of intraspinal injections of salvarsanized serum. In early cases many have been completely cured of marked impairment of hearing.

Sudden loss of hearing, generally with tinnitus, no pain, no evidence of middle ear disease, in a young adult otherwise healthy should be regarded as almost certainly indicative of syphilitic disease of the eighth nerve and labyrinth. The high-toned forks will be those least appreciable, and the watch, acoumeter and Galton whistle will elicit little, if any, response, yet conversation may be heard. However, in the marked shortening of bone conduction we have one of the most striking and reliable evidences of luetic infection, as it is perhaps the most common sign, occurring in 95 per cent of the cases. A deafness without apparent middle ear trouble showing a positive Rinné should at once arrest the attention of any aurist. In the presence of other signs of syphilis, the diagnosis will present no difficulties, but in their absence, it is not usually easy. As a rule both ears are involved though one may be so much worse that the other may appear normal, but this deception soon becomes evident, as the deafness is rapidly progressive, and the bilateral nature of the trouble is soon disclosed. Therapeutic means of diagnosis, useful elsewhere, are practically useless here, as syphilitic deafness is notably intractable, though the Swift-Ellis treatment is an exception to this rule, and may prove diagnostic as well as curative. No assistance in diagnosis is lent by the appearance of the drum, as it is not affected in any characteristic way; whereas a coincident suppurative condition, or a preexist-

ing catarrhal condition of the tympanum may actually obscure the etiology. Either condition will demand consideration where it coexists with a syphilitic process. Inflation will not improve the hearing except in the presence of some tubal or catarrhal complication, and may even increase it. Facial palsy is a rare complication, and occurs occasionally in the secondary stage associated with labyrinthine syphilis, and practically never in the third period (Lannois).

Our knowledge of the morbid anatomy is most limited and comprises the observations of a few cases at the hands of so few aurists that it is not safe to base any broad statements on their findings. However, from what has been reported of the changes in the secondary stage it would seem that hyperemia of the membranous labyrinth and increased perilymphatic pressure are to be expected; later a small round-celled infiltration and degeneration of the end-epithelium in the cochlea and ampullary crests (West). In addition to these conditions Voltolini (quoted by West) found in one case of secondary syphilis circumscribed hyperostosis around the fenestra ovalis (Moos). Moos's cases showed about the same condition, but it is particularly interesting as demonstrating that it is possible to have a true labyrinthitis and the nerve trunk remain normal. Moos and Steinbrugge report a case which perhaps best summarizes the morbid anatomy in the tertiary stage. They found these conditions: enlargement of the osseous spaces in the temporal bone and in the labyrinthine capsule, enlarged marrow spaces filled with fibrous tissue, itself infiltrated with small cells and adherent to the periosteum of the labyrinthine wall in several places, bloody extravasation between the fibers of the acoustic nerve and in the cochlea, and degeneration of the ganglionic layer in Rosenthal's canal (Politzer).

Treatment

The introduction of arsphenamine was so enthusiastically exploited that its virtues were much exaggerated, even beyond what Ehrlich himself believed it was capable of accomplishing. A single dose of this highly efficient remedy may have permanently cured a syphilitic infection, though it is exceedingly unlikely, and I believe that no case was ever so fortunate. However, such

claims are occasionally made. When the indications are as set forth already in this treatise, indicating syphilis of the central nervous system, the Swift-Ellis treatment is the only one that will give thorough access to the syphilitic toxin and should be given strictly as laid down by these two observers (see also A. R. Robertson). With this exception, the routine treatment should be that which Kerrison says is the outgrowth of Fordyce's vast experience as a syphilographer, and this is as follows: a preliminary dose of grams 0.3 to a woman or grams 0.4 to a man, intravenously, as a test of such idiosyncrasy as may exist for the remedy. If no contraindications prove to exist, a week later an injection of grams 0.4 for a woman and 0.5 for a man is given. Thus five or six are given at weekly intervals, followed by a thorough course of mercurial inunctions or injections. A period of rest next ensues for six weeks or so, if the case is an early one and the symptoms have been well controlled; at the end of this time a Wassermann test is made. If this proves positive, the whole procedure is repeated until a negative result is obtained.

It has been insisted that the use of this remedy has increased the nerve lesions, and the writer has reported a case that seemed certainly an arsenic neuritis. However, many observers of note deny this, and the controversy is well discussed in all its aspects by Benario, Duel, Alexander, Finger and many others.

The treatment of all stages is the same, and local lesions are to be treated as already indicated, or otherwise appropriately as they would be in a nonsyphilitic subject. The Swift-Ellis method should always be kept in mind where keratitis and sudden deafness arise, and a lumbar puncture done to determine the presence of pathognomonic changes in the spinal fluid.

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CHAPTER XX

CONGENITAL SYPHILIS

Inasmuch as it is now generally believed that the child which suffers from syphilis at birth is really infected in utero it is obvious that the expression "hereditary syphilis" must fall into disuse and that the term congenital syphilis is the correct one.

In dealing with the subject of congenital syphilis much trouble will be avoided if we remember that congenital syphilis is caused by an infection with the same organism that is found in acquired syphilis, and that the results of this infection are very similar. For this reason it is possible to write concerning the symptoms and pathology of the disease at much shorter length.

Infection

It is almost universally conceded that the prenatal infection is placental in origin, in spite of the fact that Finger, Neumann, Lang and Hochsinger[1] have been able to produce specific lesions in animals by the injection of seminal fluid, an experiment invalidated by the complex structure of the fluid. Nor does the fact that some women have undoubtedly been infected by the seminal fluid of men, as Boardman[2] contends, prove that children are infected through such an agency, inasmuch as it is difficult to believe that an ovum containing a treponema could develop. In a recent paper Wile[3] contends that syphilis is frequently of paternal origin, and Schamberg[4] agrees with him. Wile states: "With regard to placental transmission, the weight of evidence is more in favor of a fetal infection of the placenta than of infection of the placenta by the mother. The complement-binding substances passing through readily from the fetus to the mother, suggest an explanation for the uniformly positive tests in the mother and the otherwise inexplainable phenomenon that most such mothers go through life Wassermann-positive, without ever having clinical syphilis." Wile's beliefs were riddled by various men who discussed his paper. It has been shown, as

Glomset[5] well states, that various other infectious diseases are transmitted by the mother through the placenta to the child. Schaudinn,[6] Trinchese,[7] Frankl,[8] Graefenberg,[9] Bab,[10] and others have found treponemata in the placenta, usually in the fetal portion, although Trinchese and Hübschmann[11] have found them in the maternal portion as well. From a study of the literature Glomset believes that infection usually, but not invariably, takes place late in the course of pregnancy.

Formerly it was taught that when a nonsyphilitic mother, or a mother showing no evidences of syphilis, bore a child suffering from congenital syphilis, she was henceforth immune from the disease (Colles' law). This law is no longer held valid, because it has repeatedly been found that such mothers almost invariably show positive Wassermann reactions. It was also formerly believed that when a healthy child was born of a syphilitic mother the child could not acquire syphilis. This was known as Profeta's law. It has also been found that such children very frequently show positive Wassermanns: hence are in all probability suffering from a latent form of lues.

Syphilis of the Placenta

Correa-Dias,[12] Schwab[13] and Williams[14] have shown that a syphilitic placenta is much larger than a normal one. Fränkel[15] called attention to the changes in the chorionic villae in 1873. When they are teased out in salt solution they are seen to have become much thicker and more club-shaped than is normal. Microscopically there are characteristic syphilitic changes in the blood vessels, and that the stroma cells are closely packed, instead of being stellate. Plass[16] has recently confirmed these findings.

Frequency

It is a well-known clinical fact that by no means all syphilitic parents bear syphilitic children. Every syphilographer realizes how frequent it is to have under his care a man who has acquired syphilis ten or fifteen years before, who has had a totally inadequate course of treatment, and yet who has children that show neither the clinical nor laboratory signs of syphilis. In many instances this can certainly be explained by the fact that the

mother of the children has remained unaffected. Just what percentage of children born of syphilitic mothers are affected is as yet uncertain. However, certain it is that when a woman has active syphilis it is unusual for her to bear healthy children. One of the most marked effects of syphilis upon the fetus is the interruption of pregnancy: it is rare to find a syphilitic woman who has not had from one to five miscarriages. Kassowitz[17] states that over forty per cent of the pregnancies result in miscarriages. Lynch and McInnes[18] have emphasized the importance of syphilis upon the resulting fertility of the women, and my hospital experience has been identical with theirs. It is frequently noted that the first pregnancies following a syphilitic infection are prone to result in miscarriages, that the next child may be born dead, and that the next child may die soon after birth. In other words the children conceived soon after infection have a much worse immediate prognosis. In my own experience about 3 per cent of all syphilitic patients seen in private practice are affected with the congenital form of lues, while in dispensary practice the figures run between 8 and 10 per cent. It is certain that many more cases would be seen if it were not for the fact that there are so many miscarriages and so many early deaths.

Clinical Course

Many authorities divide congenital syphilis sharply into two great groups, that group showing early manifestations, and that group not showing lesions until after the age of puberty. Fournier has directed particular attention to the latter, calling it syphilis hereditaria tarda. In reality while this classification may be useful clinically yet pathologically it is analogous to acquired syphilis, for as has already been emphasized it is not unusual to find that after a very mild early course severe late lesions may develop after the lapse of many years.

For years it has been the custom to blame various malformations in the child to the effects of syphilis. For instance flat foot, scoliosis, and various other of the bone deformities, congenital heart disease, hernia, deaf-mutism, malposition of the viscera and many other troubles have been laid at the door of syphilis. Now as a matter of fact a child is either syphilitic or not

syphilitic, and it is extremely improbable that any of these dystrophies are caused by lues.

It is usual for the syphilitic manifestations to appear shortly after birth: ordinarily the child when born appears healthy. Miller[19] in a study of one thousand cases noted that the time of the appearance of lesions was as follows:

First week,	8.5 per cent
Second week,	13.8 " "
Third week,	24.0 " "
Fourth week,	17.7 " "
Second month,	22.0 " "

The lesions seen early in the course of congenital syphilis do not differ materially from those seen in the same stage of acquired lues. There is usually an eruption, mucous patches, some glandular enlargement, condylomata and frequently a marked alopecia upon the back of the head where it has rubbed upon the pillow. However, there are a number of other features that must be considered. There is usually more systemic disturbance than is found in the acquired type of the disease: the child rapidly becomes poorly nourished and is frequently very fretful. Very often there is a marked rhinitis that gives rise to "the snuffles." The face often looks drawn and pinched, and there may be rhagades from the corners of the mouth. A little later gummous changes may develop in any organ. The bone changes are somewhat different from those occurring in acquired lues and will later be described in detail. Dactylitis is more common. At times there will be no early manifestations noted and gummata will be the first lesions observed, they rarely appearing before the child is two years of age.

Early Cutaneous Manifestations

A pure macular type of eruption is rather uncommon, but nevertheless may occur. More commonly the lesion is either maculopapular or distinctly papular. While many of the authors speak of the maculopapular lesion as being the most common, it seems to me that they are really referring to the discoid papular type, for as a rule there are white scales upon the lesions, a finding that does not occur in the true maculopapule. While

this eruption may be generalized as in the acquired type it is not infrequent to find that the lesions are more circumscribed. They have a special tendency to occur upon the buttocks and

Fig. 124.—Children suffering from congenital syphilis not infrequently show a maculo-papular eruption, together with a few superficial ulcerations.

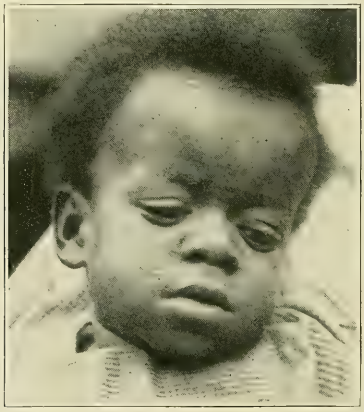

Fig. 125.—Annular lesions may be found in the negro children suffering from congenital syphilis. (Courtesy Dr. E. P. Copeland.)

around the diaper region. Upon the palms and soles there may be an erythema with a slight amount of scaling, that is not absolutely characteristic but which is extremely suggestive. In some exceptional instances there may be a generalized, mildly

Fig. 126.—Typical condylomata are not rare in congenital syphilis. (Collection of Dr. E. R. Strobel.)

Fig. 127.—Large superficial lesions may develop about the anus, and are at times called "giant condylomata."

exfoliating dermatitis. As a general rule, however, the eruption is very similar to that already described in the chapter upon early cutaneous manifestations.

Lenticular papules are uncommon but at times do occur. In

the negro typical annular lesions may appear upon either the face or body.

Superficial pustules are extremely rare, but it is not unusual to find a few scattered ecthymoid pustules. Again these resemble those found in acquired syphilis.

Vesicular lesions are rare, although they may occur in connection with bullous lesions. Grindon[20] has recently described two cases. According to him Rollet[21] was one of the first to describe this condition, and Crocker,[22] Adamson,[23] Taylor[24] and others have described cases. The vesicles may be either generalized or localized, and vary in size from one-twelfth to one-third of an inch. While the lesions are usually closely grouped, nevertheless they do not coalesce as in eczema.

Bullous lesions, the syphilitic pemphigus, are not as common as the majority of text books would have us believe. In over two hundred cases of congenital lues I have encountered this condition but once. The bullae are most common about the hands and feet and the adjacent portions of the limbs, but may occur upon any portion of the body. In size they may reach well over an inch. They may be either distended or flaccid, and the contents may be either clear or cloudy. The base is usually raw. They are frequently surrounded by an inflammatory areola. Such lesions must be distinguished from both pemphigus and bullous impetigo, and the clinical diagnosis may depend upon finding other manifestations of syphilis, usually not a difficult procedure.

Condylomata are frequently found about the perineum and anal region, and may reach a very considerable size.

Late Cutaneous Manifestations

As a general rule it may be stated that the late cutaneous lesions of congenital syphilis are comparable to the lesions developing in the course of late acquired syphilis. However, the gummous lesions are the most common. It is rather unusual to see the serpiginous nodular lesions that are so often encountered in the acquired type of the disease. The destruction resulting from ulcerating gummata is often very extensive, and the lesions

may be extremely intractable to treatment according to the statement of most syphilographers. Squamous syphilides of the palms and soles are very rare.

Cutaneous Complications

The cutaneous complications of congenital syphilis differ in no way from those described in the chapter dealing with the subject of these disorders as the result of acquired syphilis.

Fig. 128.—Gummata may appear in apparently well-developed children.

Affections of the Mouth and Throat

Mucous patches are extremely common in congenital syphilitics. They are identical with those affecting persons with acquired syphilis. The other lesions occurring within the mouth are to all intents and purposes identical with those already described. However, special attention must be directed to the teeth, for here are found certain characteristic changes. Hutchinson[25] who first described the teeth changes, and who has since paid special attention to the subject states: "The milk teeth are never characteristically malformed. * * * It is quite true that the milk teeth in syphilitic children are often very peculiar. * * * Sometimes the tooth sacs suppurate, and the crowns of the teeth, almost always the upper central incisors, are exfoliated before they are cut. The occasional occurrence of this is one of the

strongest facts which I can adduce in support of the assertion that the gums and tooth sacs are liable to congestion and inflammation during the secondary stage of syphilis in infants. I have never witnessed this suppurative exfoliation of the upper incisors excepting in those who were syphilitic. The lower incisors (second set) usually present serrations only, that is, two small notches and three elevations. I have, however, seen several examples of a single central notch, resulting apparently from the suppression of the middle denticle, as in the upper set. A far more common event than exfoliation is caries, and it is often very peculiar in form. The neck of the tooth is attacked, and is rapidly eaten

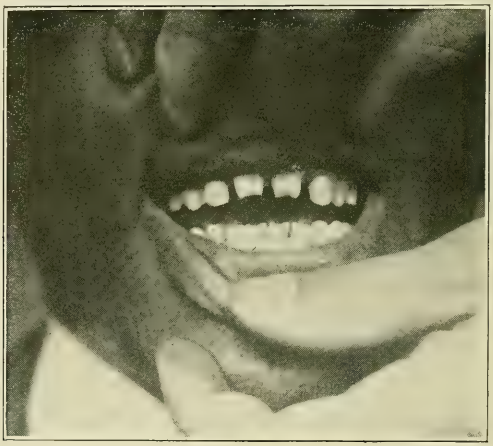

Fig. 129.—The notching in Hutchinson's teeth is characteristic.

through, and the crown drops off. In this way all the incisors of the upper jaw may be destroyed, and the child, from the age of two to that of six, may be without teeth in this position. Sometimes the lower incisors also are affected, but more rarely."

It should also be mentioned that in the case of children suffering from congenital syphilis the teeth are frequently late in erupting.

The typical "Hutchinson's teeth" of congenital syphilis are the upper middle incisors of the second or permanent set. Typical teeth have a single central notch in the center: the tooth is usually small both in length and width, and is not flattened out

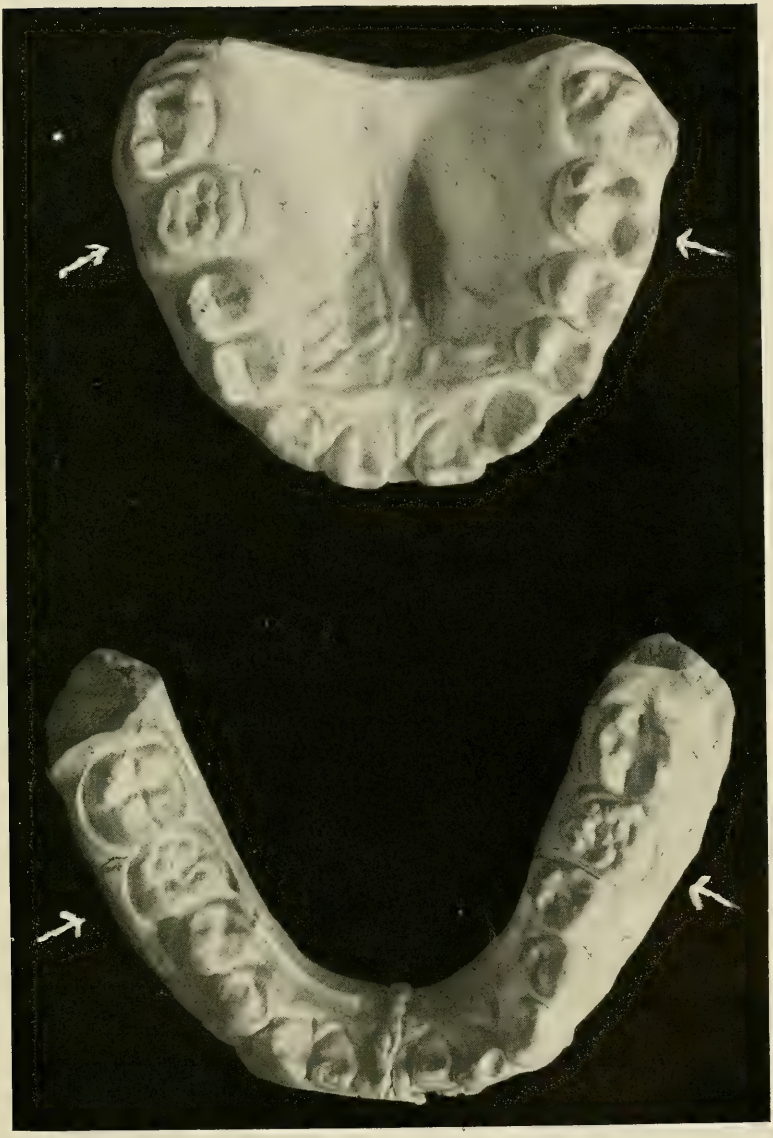

Fig. 130.—Just as characteristic as the Hutchinson's teeth are the "mulberry molars" of congenital syphilis. (Collection of Dr. Jos. S. Wall.)

as is normal, but is frequently rounded or peg-like. Still[26] has reported similar changes in the canine teeth in one case. Stein[27] has written the best recent article upon the teeth in inherited syphilis.

Dr. Jos. S. Wall (Arch. of Pediat., October, 1917) has recently called attention to very important changes which occur in the six-year molars. He has found that these teeth show changes much more regularly than do the central incisors, and that the changes are even more characteristic. To quote Wall: "There is an erosion, not the erosion of wear only, but a disintegration of the grinding surface, to which this term is applied in the absence of a better one. This erosion is irregular in form, the surface of the molar for a third or half or even the whole surface is pitted, excavated and discolored. There is often a pulpy looking mass of a dirty yellow color occupying most of the face of the crown, margined, as it were, by the line of cusps ordinarily found on the molar teeth. The tooth has been called the 'honeycombed molar of hereditary syphilis.' We have spoken of it in our clinics as the 'mulberry molar,' likening the worm-eaten center of the cutting surface to the appearance of the tip of a mulberry."

In regard to syphilitic lesions of the throat it is only necessary to say they are similar to those of acquired syphilis.

Affections of the Hair and Nails

In some few cases of congenital syphilis the hair may grow very rapidly and be very dark in color, and has been designated by Hutchinson[28] as the "syphilitic mop." Still says that this has occurred in four per cent of his cases. Still further says that in six per cent of his cases there has been a marked alopecia, especially over the vertex. In a number of hospital cases I have seen a complete baldness upon the whole back of the scalp, and am inclined to believe this to be rather common. The hair of the eyebrows may be lost as well.

The nail changes are very similar to those of acquired lues.

Affections of the Respiratory System

Syphilis of the Nose.—Diday supposed that syphilitic coryza was due to the presence of mucous patches within the nose, but

such is not now believed to be the case. Frequently shortly after birth it is noted that the child develops a coryza or "snuffles." This is a purulent rhinitis, that frequently becomes offensive. The child has a peculiar snorting inspiration, and frequently holds the head back to aid in respiration. Suckling is always interfered with. Still claims that coryza is present in 70 per cent of the cases. The upper lip often becomes eroded, and the mucous membranes of the nose may become permanently atrophied. This form of syphilis does not lead to saddle nose, which is always due to gummous changes. The gummous lesions are in no wise different from those of tertiary acquired syphilis. I have recently seen a case where a gumma of the nose developed in an apparently healthy girl of twenty. Further investigation showed that the other children in the family were suffering from congenital lues.

Syphilis of the Larynx.—Still claims that 14 per cent of his cases showed hoarseness. This may be due either to a simple inflammation or to actual ulceration. These children may have attacks of laryngeal spasm, and some "crowing" is frequently observed. The subject has been studied by Carpenter,[29] Sharp,[30] Garel,[31] Mackenzie[32] and others.

Syphilis of the Trachea and Bronchi.—Connor[33] in his excellent review of the literature upon this subject found 10 cases of congenital lues as opposed to 118 cases of acquired form. The symptoms are the same in either form of the disease.

Syphilis of the Lungs.—The best known condition is the pneumonia alba, found in stillborn children, and which was first described by Virchow. The lungs are usually nearly airless, but are increased in size. Both lungs may be affected throughout or but a small portion of a lobe may be involved. On section the lung tissue is firm and white, or may be mottled gray and red; the cut surface is smooth. Microscopically the interstitial tissue is not increased, although the alveolar walls are thickened. There is a marked infiltration of the interstitial tissue with fixed tissue cells, and the blood vessels show characteristic syphilitic changes. Large numbers of treponemata are present.

It is probable that there are mild degrees of this condition

which are consistent with longer life and in which there are pathologically fibroid changes in the interstitial tissue. Cases that suggest this have been reported by Greenfield,[34] Symonds[35] and Carpenter.[36] Still[37] suggests that certain of the cases of bronchiectasis in children may be due to syphilis. It is also probable that pulmonary fibrosis that arises in children may in some instances be due to syphilitic changes.

Gummata are usually considered rare, but Still, Behrend[38] and Barlow[39] have reported cases. The symptoms are comparable to those already discussed in the chapter on acquired syphilis of the lungs.

Syphilis of the Digestive Tract

Syphilis of the Salivary Glands.—There are but five cases reported in the literature. Haslund[40] has recorded one early in life where there was an acute inflammatory swelling. The other four cases were gummata that occurred late in the course of the disease. These were reported by Erler,[41] Mandowsky,[42] Cassel[43] and Feldmann.[44] Gerber's[45] article contains a complete bibliography.

Syphilis of the Esophagus.—Wile's[46] excellent article upon esophageal syphilis makes no mention of the congenital type of the disease, although he reviews the literature very thoroughly. It is probable that cases have escaped recognition.

Syphilis of the Stomach.—So far only pathologic reports of congenital gastric syphilis are available. These have been made by Chiari,[47] Flexner,[48] Gaillard,[49] Büttner[50] and others. All agree that either the whole stomach wall or merely portions of it may be involved, and that usually it is involved throughout its entire thickness. Miliary gummata, with syphilitic changes in the vessels and some diffuse infiltration are found.

Syphilis of the Intestines.—While congenital syphilis of the stomach seems to be rare that of the intestines is much more frequent, although all of our reports come from the autopsy room. Councilman[51] has reviewed the reports of Kundrat and Mrazek, Baumgarten, Wagner and Chiari. He states that the lesions are usually found in the small intestine, but that they may occur in the large. In general there are two forms, one

where only the Peyer's patches or solitary glands are involved and one where the disease is scattered irregularly throughout the whole of the small intestine. The histologic findings are similar to those occurring in the stomach. At times there may be an adhesive peritonitis. Other cases have been reported by Fraenkel[52] and by Büttner.[50]

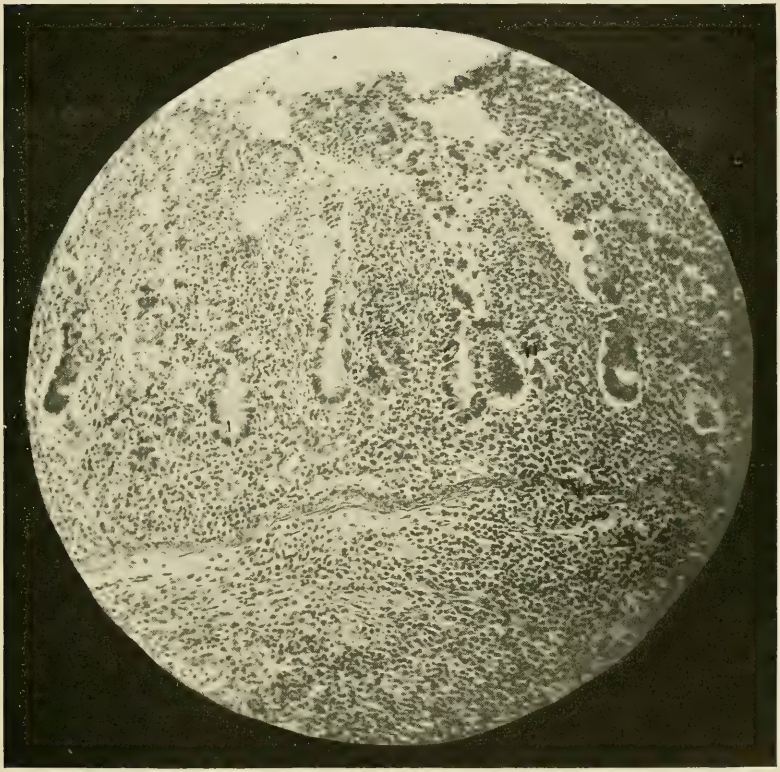

Fig. 131.—In congenital syphilis the intestines may show changes that resemble those in other organs. (Collection of Drs. Fordyce and MacKee.)

Syphilis of the Liver.—Rolleston[53] gives an excellent account of congenital syphilis of the liver. Gübler[54] first described the disease in 1852. Lancereaux[55] gives an admirable historical review of the subject. Hepatic syphilis is extremely common in congenital syphilitics, Hofmeister[56] putting the figures at 39 per cent and Feige[57] at 65 per cent. Rolleston con-

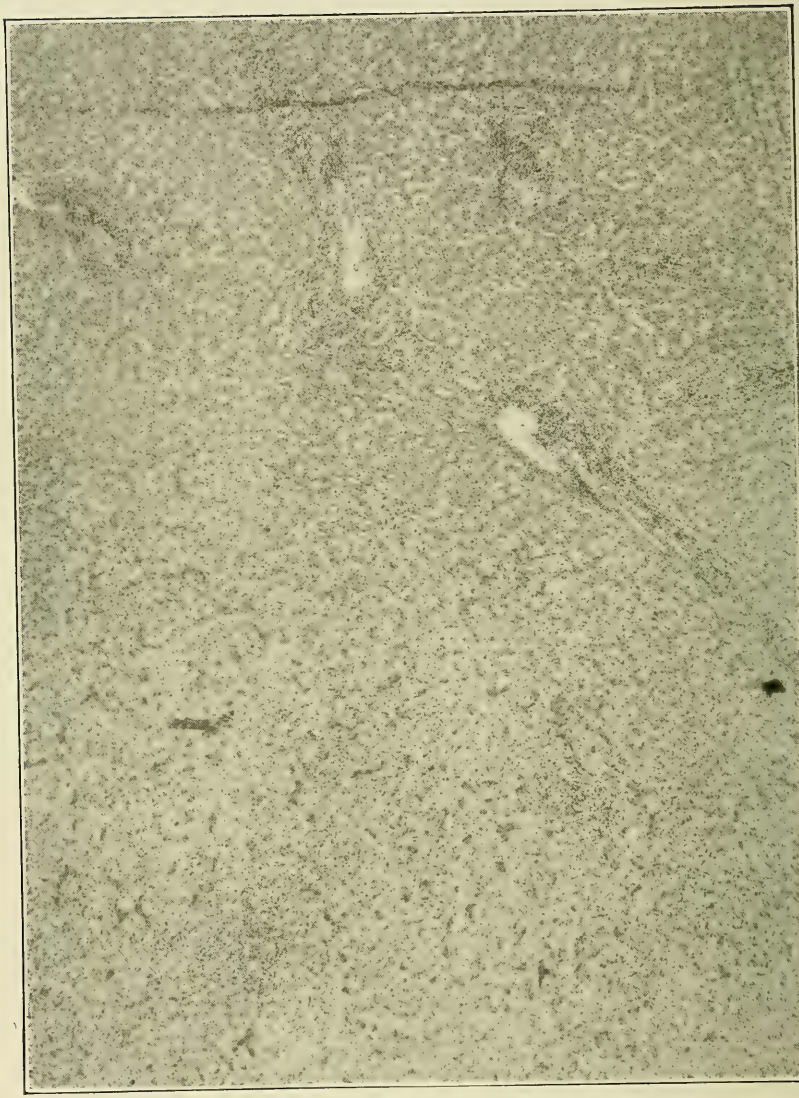

Fig. 132.—In congenital syphilis the liver is frequently involved. The first changes are interstitial in character. (Collection of Drs. Fordyce and MacKee.)

siders that there are three main types, that occurring at the same time that the secondary manifestations appear, the tardive type, and the multilobular cirrhosis that supervenes in later life. In the first type the child may be born healthy and

the lesions develop rapidly, or the child may be stillborn. There are usually signs that point to liver disease, such as an enlarged liver, although jaundice and ascites are frequently absent. The liver is firm and tender: at times there is a localized tumor formation, but this is rare. The spleen is frequently enlarged as well. When jaundice does occur it may be due to

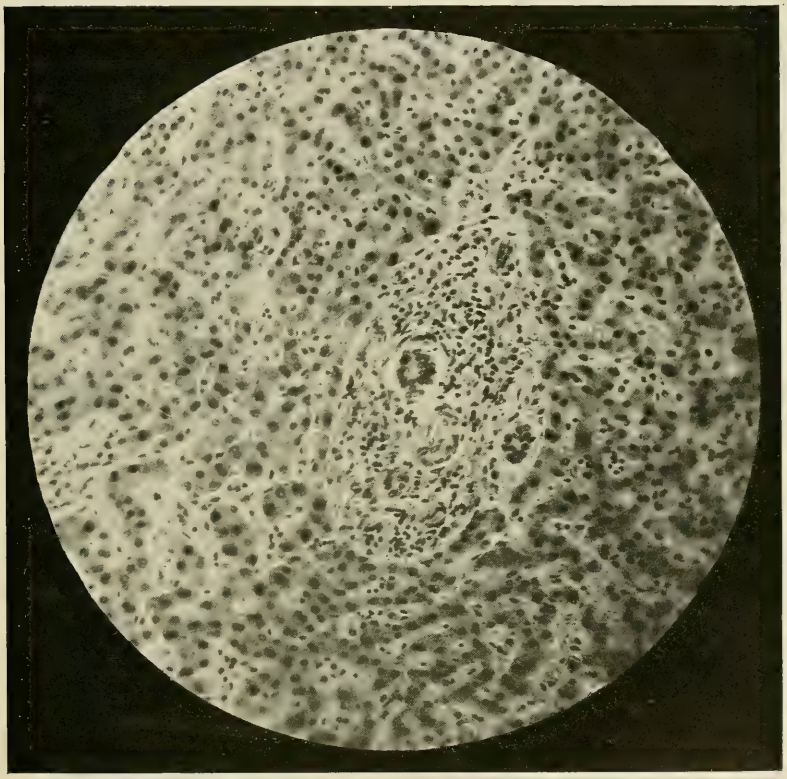

Fig. 133.—Under the high power, the characteristic syphilitic infiltration can be well seen. (Collection of Drs. Fordyce and MacKee.)

secondary infection as Milon[58] has pointed out. Pathologically the changes are usually diffuse: the surface may show adhesions, but usually the surface is smooth. On section it is firmer than normal, and there is some mottling due to some portions being more affected than others, there being yellowish areas. Small gray spots are usually to be distinguished; these are small

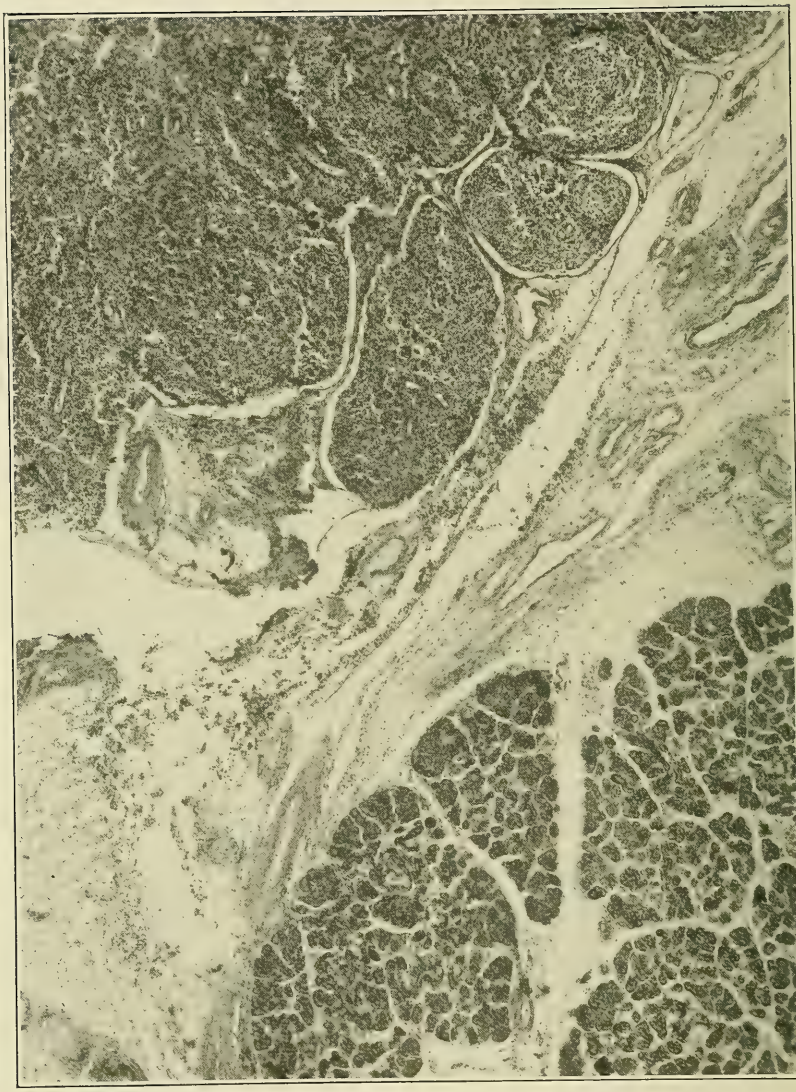

Fig. 134.—The pancreas can be involved in congenital syphilis. (Collection of Drs. Fordyce and MacKee.)

gummata. Microscopically there is a proliferation of the connective tissue elements, and of the endothelium of the capillaries and lymphatics inside the hepatic lobules. Characteristic changes around the larger vessels are usually to be made

out. As a late stage it is found that the individual liver cells may be separated one from the other by the proliferated fibrous tissue. Still later there may be well-marked bands of fibrous tissue that transverse the organ.

When the hepatic changes do not occur until a late date they are comparable to those of late acquired syphilis. The disease is not very rare: cases have been reported by Wilks,[59] Morris,[60] Fournier,[61] Hudelo,[62] Forbes,[63] Mackenzie[64] and others. Lardaceous changes frequently complicate the picture.

The parasyphilitic multilobular cirrhosis is not a result of the ordinary pericellular cirrhosis so common in early life. The multilobular cirrhosis usually comes comparatively late after birth, often not for many years. The clinical features are those of portal cirrhosis in children, namely, portal obstruction, ascites and wasting. Cases have been reported by Lazarus-Barlow,[65] and others.

Syphilis of the Gall Bladder and Gall Ducts.—There are no cases upon record of syphilitic involvement of the gall bladder. However there are two cases of congenital stenosis of the ducts due to syphilitic deposits, those of Beck[66] and Rolleston.[67]

Syphilis of the Pancreas.—There are upon record numerous cases of specific involvement of the pancreas in congenital syphilitics. Oser[68] gives an admirable review of the subject. He states that Birch-Hirschfeld found changes in 23 cases, and that out of 124 cases the pancreas was involved in 27 instances.

Hecker also found similar changes in 22 per cent of his cases. A chronic indurative pancreatitis was the lesion usually found, but miliary gummata have also been described. Klebs has found frank gummata. Marshall[69] has suggested that a pancreatitis due to syphilis may be the cause of some cases of diabetes found in the young. Others who have written upon this subject are Heubner,[70] Condon,[71] Pearce,[72] and Schlesinger.[73]

Syphilis of the Vascular System

Syphilis of the Pericardium.—But little is to be found in the literature upon syphilitic pericarditis. It is true that gummous processes may extend through from the myocardium, and Wanitschke[74] has shown that they may also extend from the mediastinum.

Syphilis of the Myocardium.—Syphilitic lesions of the myocardium have been well described by Warthin,[75] on a basis of fifty cases that he had studied. He divides the lesions into parenchymatous and interstitial, just as in the cases of acquired cardiac syphilis. Treponemata are frequently found either in the tissue spaces of muscle areas, or about the blood vessels, without any demonstrable lesions. Pale degeneration of the heart muscle is also found. At times fatty degeneration or simply atrophy occur. In regard to necrosis he states: "In virulent cases of congenital syphilis in which the tissues of the body show enormous numbers of spirochetes, yellowish or light-colored areas may be found in the myocardium as well as in other parts of the body. These areas rarely exceed 5 mm. in diameter, and are usually smaller. In the heart the muscle in these areas appears as fine fibrillæ without nuclei, or is entirely absent, its place being taken by a collection of lymphocytes, plasma cells, and fibroblastic cells. Around the borders fibers showing transition stages of liquefaction are seen, and the surrounding tissue appears as in chronic edema, the tissue elements being pushed apart and the spaces filled with a fine albuminous precipitate, a mucoid substance and cells. * * * Such changes are absolutely independent of any vascular changes, and wholly the result of the spirochetes that lie packed in great numbers in these necrotic areas."

There are a number of types of interstitial changes. The first is edema, in which moist and translucent pale areas may be seen with the naked eye, and which microscopically show edematous changes. These spaces contain great numbers of treponemata, and a mucin-like substance is present. Interstitial proliferation is primarily vascular or perivascular, and can be interpreted as typical syphilitic changes. "In the congenital cases caseation of these areas must be very rare, as we have never found it. * * * A striking finding in the hearts of congenital syphilis is the occurrence of round, translucent areas that microscopically suggest myxomas and have been mistaken for such. With ordinary stains, hematoxylin and eosin, they appear as sharply circumscribed, spherical areas in which the heart muscle has completely disappeared, only a few atrophic fibrillæ being left. A gelatinous tissue

Fig. 135.—In the heart the syphilitic changes may be either interstitial or directly in the muscle fibers. (Collection of Drs. Fordyce and MacKee.)

containing branching epithelioid cells and lymphocytes forms the main part of the area and new capillaries occur in it. Mucin tests show the presence of a large amount of mucin, so

that the resemblance to a myxoma is greater still in preparations attained in this manner. Levaditi preparations show the presence of spirochetes in varying numbers in these areas, although the number is usually not so great as in the focal fatty areas and edemas. It is probable that the infection is a less virulent and more sharply localized one. These areas may be regarded as young or undifferentiated gummata, myxoma-gumma, without fibroid change or caseation, the tissue remaining in a fibroblastic semigelatinous state. The infiltration with lymphocytes and plasma cells is often very slight, so that this adds to the deceptive appearance of this formation, and if the Levaditi method for the demonstration of spirochetes was not carried out, the true nature of the process would not be detected."

Other observers have reported the presence of true gummata in the heart muscle of congenital syphilitics.

Endocarditis and Diseases of the Valves.—The literature has but little to say in regard to syphilitic endocarditis; however in view of the immense number of organisms in a child with congenital lues it seems certain that the endocardium can not escape damage in all cases. In view of the well-known fact that congenital syphilitics suffer from specific arteritis they must at times have aortic insufficiency. Anders[76] calls attention to this fact.

Heart Block.—Nanta[77] and Saundby[78] have both reported cases of heart block developing in persons suffering from congenital syphilis.

Arteritis.—Typical syphilitic aortitis may be induced by the treponema in congenital syphilis, as Klotz[79] has shown. As a result of these, aneurysm may develop as both Le Boutillier[80] and Osler[81] have emphasized.

Raynaud's Disease.—It has already been pointed out that there is great confusion in the literature as to the differentiation of Raynaud's disease from arteritis, especially syphilitic arteritis. Cases of so-called Raynaud's disease in persons suffering from congenital lues have been reported by Hutchinson,[82] Marsh,[83] Humphrey,[84] Duckworth,[85] and many others. Lisser[86] has recently added another case and given a complete bibliography to date.

Syphilis of the Veins.—Thompson[87] states that the veins in those suffering from congenital syphilis are often weak, and that marked dilatation of the superficial veins of the scalp is often noted in young infants. I have seen several instances of severe forms of angiomata in the syphilitic negro, in whom angiomata are very rare.

Syphilis of the Blood.—It is a well-known fact that there is often a marked secondary anemia in connection with congenital lues. Chiaravalloti[87a] has examined the blood of 150 cases and found that the hemoglobin varied from 12 to 75 per cent, with a corresponding decrease in the number of red blood cells. It is usually stated that a high lymphocyte count is the rule, but I[88] have been unable to confirm this finding, only one of my five cases showing a high count. Hochsinger[89] has also studied this question.

Syphilis of the Spleen.—That syphilis of the spleen is common in congenital syphilis has been recognized since the publication of Gee's[90] paper in 1867. In 1877 Barlow[91] confirmed this observation. Coutts[92] found the spleen enlarged in 62 out of 100 cases, and Still[93] states it is easily palpable in 45 per cent of the cases and at least one inch below the costal margin in 22 per cent. There are three types of lesion, the simple hyperplasia, the diffuse fibroid changes, due of course to miliary gummata, and the true gummata, examples of which have been reported by Still[94] and others. Hutchinson[95] has also reported several cases of splenic syphilis.

Syphilis of the Lymph Glands.—It is generally considered that the superficial lymph glands are not so constantly enlarged in congenital as in acquired syphilis, a point with which I agree thoroughly. However, during the early stages it is usually possible to find a number of such glands, and in almost every case I have found that the epitrochlear glands were palpable. This at times may be a valuable diagnostic point. True lymphomata have been reported by Still,[96] Holt,[97] and others.

Melena Neonatorum.—Some have attributed hemorrhage of the newborn to syphilis: among these are Abt[98] and Wilson.[99]

Fig. 136.—The spleen is often involved. (Collection of Drs. Fordyce and MacKee.)

However Machell[100] could find no evidence of it in fourteen cases, and the work of Whipple[101] and others would seem to show that the true melena is due to disturbance in the coagulation.

Syphilis of the Bones, Joints, Muscles, Tendons, and Bursæ

In general it may be said that the lesions of the bones, joints, muscles, tendons and bursæ in congenital syphilis are very similar to those occurring late in the acquired form of the disease: however there is one lesion that is characteristic of congenital lues, namely osteochondritis.

Syphilis of the Bones.—While osteochondritis (epiphysitis) is unquestionably the characteristic osseous lesion of congenital syphilis, still periostitis and osteitis do occur and not rarely. Dactylitis is also fairly common.

Periostitis may occur at practically any stage of the disease and is in reality a counterpart of the type found in the acquired form, although there may be rather more deformity. The tibiæ are probably more frequently affected than are any of the other bones, and the well-known "sabre tibiæ" may result, they being due to a marked convexity of the anterior edges. The usual course of the disease is for the subperiosteal gummata to calcify, but ulceration to the exterior may result.

Osteitis and osteomyelitis are similar to the conditions already described in the chapter on acquired syphilis of the bones. However, the skull bones are not so frequently affected, while the nasal bones are more frequently involved.

Parrot[102] has described bossing of the skull as due to lues. A typical text book case should show four thickened, rounded elevations at the vertex of the skull surrounding the anterior fontanelle: at times, however, only two are present. Coutts believes that four bosses indicate syphilis, but Still[103] can not concede this point. Rickets may give a similar condition.

By craniotabes various observers mean various conditions: some mean simply a diffuse yielding of the edges of the parietal bones on pressure, while others limit the term to islands of parchment-like bone surrounded by well ossified areas. In either condition Still believes that rickets is the most frequent cause, despite the opinions of Barlow and Lees,[104] who reported 47 per cent as due to lues and Carpenter[105] who considered 74 per cent as luetic.

Dactylitis is not infrequent: Still gives an incidence of 2 per cent. In the vast majority of instances it occurs before the age

of two is reached. The proximal phalanges of the fingers are usually affected, but the toes may be involved, and in one or two cases the metatarsals have been affected. Clinically there are usually several fingers involved, and the disease may be uni- or bilateral. A fusiform swelling slowly develops and it is unusual for this to soften or break down. The condition has been variously considered as due to periostitis, epiphysitis and to osteitis or osteomyelitis. It must be distinguished from tuberculosis, and here the age of the patient, as well as the various clinical and laboratory signs will aid in making a correct diagnosis.

Fig. 137.—Children frequently show dactylitis. (Collection of Dr. Richard L. Sutton.)

Osteochondritis was first described by Wegner[106] in 1870. Many men have written on the subject, but one of the best descriptions is that by Post.[107] According to this observer three types of lesion occur. The most characteristic and typical occurs along the line of ossification; the single line of demarcation becomes thickened and enlarged. In advanced stages a subluxation may occur. In addition there is frequently some periostitis, and also certain changes in the marrow, which may be responsible for the anemia that sometimes accompanies congenital lues. Osteochondritis frequently results in the stunted growth of the long bones. The pseudoparalyses of Parrot are not infrequent accompaniments of the disorder. Usually there

is considerable tenderness on pressure and the child cries when handled. This form of osseous syphilis is far from uncommon: Still states it occurs in from 11 to 22 per cent of all cases.

Other articles of interest are those of Addison,[108] Leroux and Labbe,[109] Losee,[110] Owen,[111] Veeder and Jeans,[112] Tubby,[113] Taylor,[114] Cumston,[115] Weber[116] and Winfield.[117]

Syphilis of the Joints.—Lesions of the joints in congenital syphilis are far from rarities as is proved by the figures of the following authors: Dunlop[118] had 16 cases, von Hippel[119] reported joint lesions in 56 per cent of his cases, Still[120] in 7 per cent. Males are more apt to be affected than are females. The following classification may be adopted: arthralgia, synovitis, hydrarthrosis, osteochondroarthritis, gummous synovitis, osteoarthritis or von Gies joint.

Arthralgia naturally can not be well recognized in young children, but tenderness on pressure may give a clue. Fournier thinks that it is rare, while the majority of other authors do not mention it.

Synovitis or pseudorheumatism is not mentioned by the majority of authors, but occurs in much the same form as in acquired syphilis.

Hydrarthrosis was first described by Clutton[121] and frequently goes under the name of "Clutton's joints." The majority of writers upon congenital joint lesions now recognize them as distinct types of congenital arthritic syphilis. These joints usually develop in early adolescence: the only sign or symptom is the presence of fluid in the joints. The knees are most frequently affected and the effusion is frequently bilateral. The synovial membrane is the site of diffuse gummata. Treatment is usually prompt in its results. It has been suggested that recovery is more rapid if the fluid be aspirated under aseptic conditions.

Osteochondroarthritis is especially well described by Gourianz.[122] This author states that it is fairly frequent and usually appears between the ages of 8 and 13. The lesions are frequently bilateral and the joints are affected in the following order of frequency, knees, elbows, hips, and ankles. The onset is insidious, claudication being the first symptom; this is due to deformity from epiphyseal hyperostosis and effusion. The effusion is clear. The synovial tissues are swollen and present

plaques upon their surfaces, but there are no fungous growths. When the lesion becomes advanced the joint is globular in shape, the skin is thinned and shows a network of blood vessels. There is no local adenopathy and no contractures or deformities.

Gummous synovitis is very similar to the type occurring in the acquired form of the disease.

Osteoarthritis or von Gies joint was first described by this author[123] in 1881. It occurs later in the course of congenital lues than do the other types described above. The condition is a multiple, progressive chondritis or chondroarthritis. Its pathology is not dissimilar to that of the atrophic arthritis of Goldthwaite. The cartilage of these joints is thinned and ulcerated, frequently leaving small islands of cartilage in an otherwise denuded end of bone. The epiphysitis is soft, and the remaining cartilage is soft and friable. The joint membranes are covered with villi, which resemble the fat pads in the ordinary types of arthritis deformans. The bone itself frequently shows other syphilitic changes. It is rather difficult for the authors to sharply differentiate this type of arthritis from osteochondritis on the one hand and from Mericamp's type of syphilitic arthritis deformans on the other. In fact there is probably no hard and fast dividing line between the conditions, and they are rather examples of degree than of any essential pathologic difference.

Syphilis of the Muscles.—There is every reason to believe that individuals suffering from congenital syphilis may show exactly the same muscle lesions as syphilitics with the acquired type. However on this subject the literature is practically silent, only Hartley[124] citing Fournier as having seen one gumma of the gastrocnemius and four of the lingual muscles.

Syphilis of the Tendons or their sheaths is not mentioned in the literature, except by Lang and Ullmann,[125] who give very little data.

Syphilis of the Bursæ.—Churchman,[126] in his extensive review of luetic bursopathies, states that there are no undoubted cases of congenital syphilis of the bursæ in the literature but that there are several suggestive cases, which he cites fairly fully. Since this time Coues[127] has reported a case, which, however, is not absolutely beyond criticism.

The Kidneys in Congenital Syphilis

By H. A. Fowler, M.D., Washington, D. C.

In early as well as late congenital syphilis, specific lesions of the kidney occur usually in association with specific lesions and congenital deformities of other organs and parts of the body. All varieties of nephritis are met with, but as a rule the kidney changes are overshadowed in importance by other manifestations of the disease. An exhaustive study of the subject may be found in the monograph of Karvonen.

Early Congenital Syphilis of the Kidneys.—Among certain of the earlier authors affection of the kidneys in congenital syphilis was considered rare (Lancereau, Polnow, Spiess). Klebs in 1876 stated that intrauterine kidney syphilis is apparently not so rare as it appears, but is generally overlooked. Negel went even further in stating that the chief cause of death in hereditary syphilitic children was either uremia or other results of the kidney disease, and Fournier states categorically that kidney diseases are common in congenital syphilis, "an undeniable fact as shown by hundreds of observations." Karvonen examined seven cases of congenital syphilis, and in all but one the kidney changes were due to syphilis. He collected 25 cases from the literature.

Symptomatology.—As a rule there are few or no symptoms referable to the kidney. The pathologic changes most commonly found give rise to no symptoms aside from depressed renal function. These children are usually underdeveloped, undernourished, anemic, and cachectic, and they show other unmistakable evidence of syphilitic taint. As is well known premature births are common among syphilitic children, and many are stillborn.

Pathology.—To the naked eye the kidney may appear normal although microscopic examination reveals definite histologic changes. The kidney may show hyperemia and punctiform hemorrhages. Occasionally whitish, or yellowish nodules may be seen scattered over the surface, and on section these nodules are found in the deeper layers. They are composed of connective tissue and some may show caseous degeneration. Miliary nodules

occurring throughout the kidney were described by Beers, as miliary syphiloma.

The following pathologic changes are described by Karvonen.

1. *Arrested Development.*—The importance of this feature is emphasized by Karvonen. Sections of the kidney showed isolated groups of cells of the embryonal type surrounded by normally developed tissue. These cell groups represent incomplete or arrested development (pseudoglomerulus). A similar process is found in the lungs and liver.

2. *Parenchymatous Nephritis.*—This form of nephritis appears to be comparatively rare in hereditary syphilis. As pointed out by Hahn great care must be taken to rule out other causes, especially mercury. And Hirsch remarks that only those cases should be considered as due to syphilis which are accompanied by other symptoms of the disease. Cases of hemorrhagic variety of parenchymatous nephritis have been reported by Hahn, Finkelstein, and Carpenter.

3. *Kidney Hyperemia.*—There is a dilatation of all the blood vessels, especially the capillaries, with the escape of leucocytes into the tissues. It is difficult to say if this is a primary syphilitic hyperemia. Probably mercury is the cause of the lesion in some of the cases.

4. *Interstitial Nephritis.*—This is the most common form seen in congenital syphilis. Changes in the interstitial tissue are observed in the majority of cases of heredosyphilis. A variety of histologic changes have been described. Karvonen found, contrary to the observations of the others, that contracted kidney is not common in heredosyphilis.

5. *Gumma.*—Gumma occur in about 6 per cent of cases. These are usually small, multiple, occurring as nodular accumulations of round and spindle cells in the coarse fibrous tissue. Some of these nodules show central caseation. Large gummata are rare.

Diagnosis.—This is seldom made during life as the symptoms are rarely in evidence on account of the nature of the lesion. In only a few cases has the condition been recognized except at autopsy.

Prognosis.—It is probable that many unrecognized cases are cured by specific treatment. The prognosis is, therefore, not as bad as the literature would suggest.

Late Congenital Syphilis of the Kidneys.—According to Fournier and Karvonen, under this heading grouped (1) cases in which the symptoms appear first after several years and (2) cases in which early congenital syphilis run their course and after a long latent period appear in a new form. While a number of cases have been reported, our knowledge of the subject is still very rudimentary and uncertain. In many cases the pathologic lesions are too complicated and involved to permit referring the various changes to their proper etiologic causes. The subject is reviewed by Fournier and Karvonen.

Treatment.—The treatment of the various lesions of the kidney occurring in heredosyphilis is in general the same as that for renal complications in acquired syphilis. Specific treatment is well borne and is aimed at the removal of the cause. Little can be expected from any form of treatment when the kidney structure has been seriously damaged in the severe grades of the disease.

Syphilis of the Female Genitals

Vulva.—Condylomata of the vulva are not uncommon during the florid stage of congenital syphilis. They are usually associated with an eruption upon other portions of the body, and with condylomata of the perineum.

The Vagina, Cervix and Body of the Uterus are not affected according to the reports of Gellhorn and Ehrenfest.[128]

Fallopian Tubes.—Doenhoff[129] has reported the case of a newborn child who died from congenital lues. The tubes were thickened throughout their entire length. Microscopically they showed syphilitic changes. Ballantyne and Williams[130] have reported a similar case.

Ovaries.—There are no records concerning syphilitic disease of the ovaries. However, according to Gellhorn and Ehrenfest treponemata have been demonstrated in the ovaries by Hoffmann and Wolters, Levaditi and Savage, Bab and others.

Syphilis of the Endocrine Glands

A considerable number of cases of luetic involvement of the endocrine glands have been reported. Unfortunately in most of these cases we have only pathologic findings, and no clinical

history, due to the fact that the lesions were discovered at autopsy. For a general discussion of the subject the reader is referred to the chapter upon acquired syphilis of these glands.

The Thyroid.—It is usually stated that congenital syphilis of the thyroid gland is rare, but this may be because it is not looked for. Demme[131] states that he has seen children with gummous nodules, and Gombault,[132] Garnier[133] and Clark[134] have reported cases. In Clark's patient there were marked symptoms of hypersecretion, no exophthalmos, pulse rate of two hundred, palpitation and extreme nervousness. Under specific medication recovery occurred.

The Parathyroids.—No literature upon this subject can be found.

The Thymus.—Adami[135] states that both gummata and diffuse fibroid changes may be found, and Hochsinger[136] believes that there may be a very marked enlargement which subsides under therapy. Possibly the Dubois[137] abscess has aroused more interest than any other lesion. Chiari[138] holds that this is a cavity lined by epithelium, and derived from accumulation of cells within a Hassal's corpuscle, but Simmonds[139] and Schlesinger think that the cyst formation is due to arrest of development of some of the epithelial tubules that give rise to the thymus. Warthin[140] has suggested that in some cases it is due to post-mortem softening of the gland. Wiesel[141] has given a complete bibliography of the subject and Oliver[142] has written a good article.

Pancreas.—Syphilis of the pancreas has already been discussed.

Testes and Ovaries.—Lesions of these organs have been discussed elsewhere.

Suprarenals.—Syphilitic lesions of the suprarenals have been found at autopsy, but the symptomatology is practically unknown. Cases have been reported by Esser,[143] Kokubo,[144] Vmogradoff,[145] Simmonds[146] and others. In a late paper Simmonds states that the most frequent pathologic change is the so-called perihypernephritis syphilitica, the process being in the capsule and associated with atrophy of the cortex. In addition gummata and necrotic areas frequently occur in the medulla.

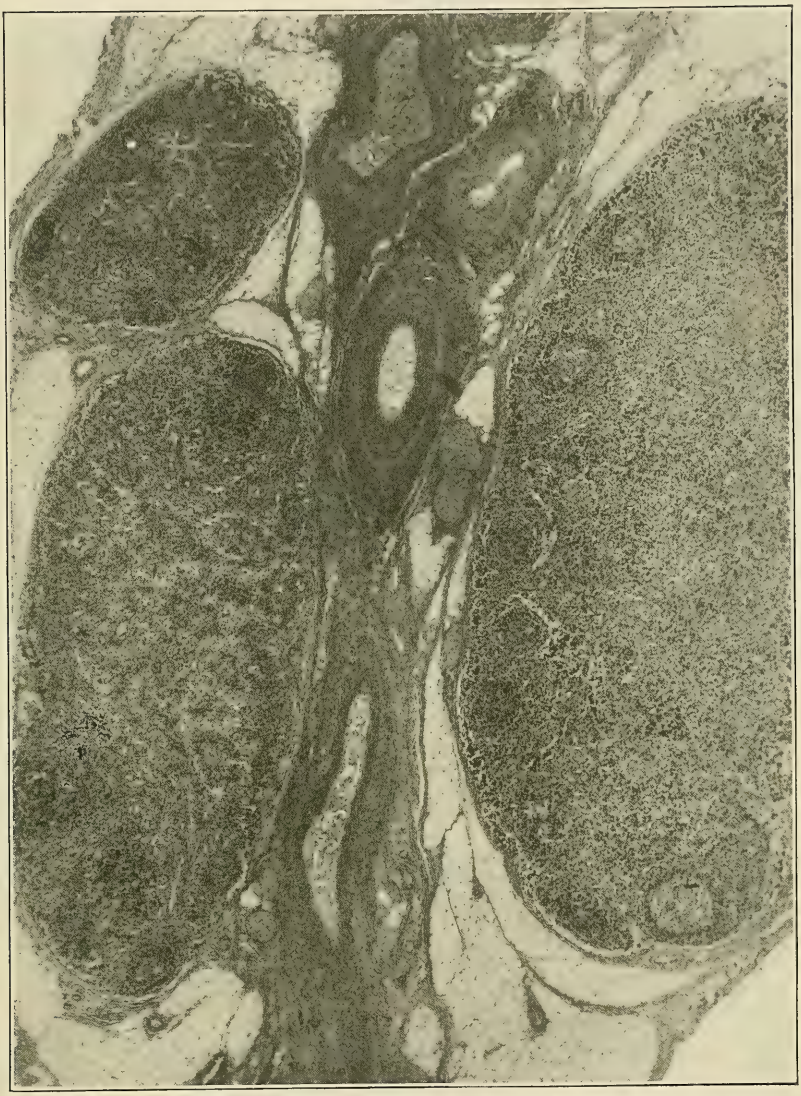

Fig. 138.—It is possible that syphilitic changes in the thymus may interfere with growth. (Collection of Drs. Fordyce and MacKee.)

Pituitary.—Lancereaux[147] states that the pituitary may be enlarged and indurated in congenital syphilis. Simmonds[148] was able to collect ten cases from the literature, those of Simmonds, Schmidt, Chiari, Triboulet, Dalpy and Hardwick. Also it is

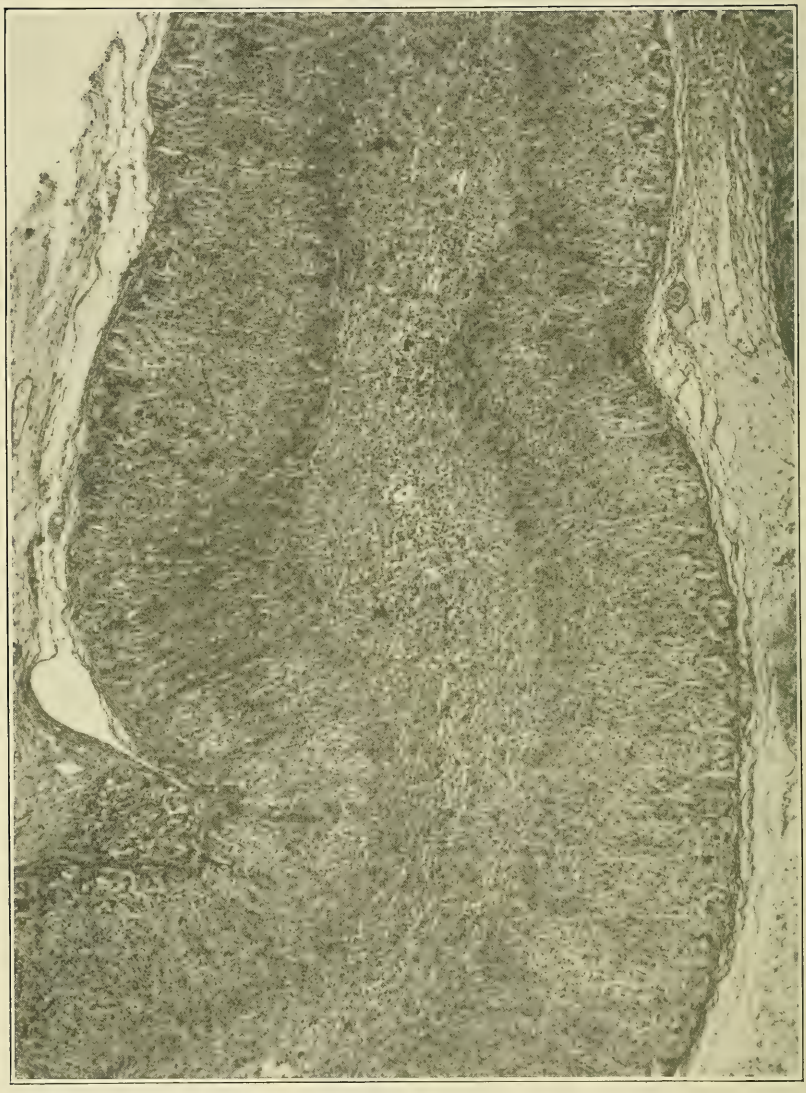

Fig. 139.—The adrenals may be badly damaged in congenital syphilis. (Collection of Drs. Fordyce and MacKee.)

probable that syphilitic disease of the pituitary can, either directly or through internal hydrocephalus, cause the adipose genital dystrophy of Bartels.[149]

In addition it is certain that various glands may be diseased

at the same time, so that various symptom-complexes result. Reede tells me that he has seen a number of such cases in congenital syphilitics which he is as yet unable to classify satisfactorily. Vagli[150] has also called attention to this fact.

Congenital Syphilis of the Nervous System

By Dr. John Lind

In congenital syphilis the nervous system is involved in 13 per cent of all cases, according to Rumpf. The symptoms are most apt to appear during the period of puberty, although Fournier reports onsets as late as the twenty-eighth year and Lepine and Charcot as late as thirty-two. The most frequent year of incidence is the twelfth.

Hochsinger in 1911 reported that he had observed 208 children of syphilitic parents and 89 had some disease of the nervous system. Practically all the forms of nervous syphilis which are discussed elsewhere (See Chapter on Syphilis of the Nervous System) can occur in children, showing essentially the same symptomatology so that it is not worth while to repeat these descriptions here. The most common forms are juvenile paresis and juvenile tabes. There are, however, other affections of the nervous system due to congenital syphilis which are not met with in the adult forms, such as certain forms of feeble-mindedness, hydrocephalus, ependymitis, Friedreich's ataxia, primary optic atrophy, Little's disease, a nervous form of rickets, simple nervousness, and amaurotic idiocy. Pure spinal syphilis is, according to Nonne, never found in congenital lues.

Congenital syphilis may occur as the result of a direct invasion of the fetal nervous tissue by the treponema pallidum. It has been found there in large numbers with an ease markedly in contrast to what is the case in the nervous syphilis of adults.

The pathology of congenital syphilis can be divided broadly into two main classes, the genuine specific changes and the nonspecific syphilitic changes. The nonspecific syphilitic

changes include groups of partially abnormal ganglion cells. Vitreous masses exist around the vessels in the central nervous system.

There is a class of children who show anomalies in physical structure—Hutchinson teeth, saddle nose, striæ about the mouth, prominent veins, scaphoid scapula, etc., and others in whom the signs are much less prominent, perhaps slight neurologic ones, but who show patent mental defect; they are silly, unable to get along at anything, yield readily to all sorts of influences. They are broadly called "feeble-minded."

Hydrocephalus is comparatively frequent in congenital lues. Syphilitic arteritis is the usual cause of this malformation. There is an exudation of lymphatic fluid in early intrauterine life causing a watery accumulation in the ventricles. Hochsinger has studied 35 cases. The usual time of onset was from the third to the eleventh month. Six cases began in the uterus. Eleven cases showed no nervous symptoms. The symptoms are disturbances of consciousness, mydriasis, myosis, vomiting, bradycardia, convulsions, pareses and muscular rigidity. Cases have been reported cured by antisyphilitic treatment.

Other brain conditions, such as ependymitis, may occur in congenital lues. The syphilitic toxin, transmitted from the parent to the fetus, comes in contact first with the developing nervous system and causes the deformities or malformations. Brain apoplexies may occur, arteritis, or disease of the meninges. The optic nerve is frequently involved in hereditary syphilitic basilar meningitis.

Occasionally a symptom-complex develops which resembles closely Friedreich's ataxia. The differentiation may be impossible and depends on the spastic symptoms, convulsions, and paralyses of the eye muscles.

In congenital syphilis a rachitic nervous picture may appear so that these children from slight causes develop eclamptic convulsions. The pathology of this is hard to explain.

Sachs described a series of cases of idiocy which he did not suspect arose from syphilis. Such cases of amaurotic idiocy usually occur in several members of the same family; post-

mortem they show disease of the cells and medullary fibers of the cortex. Spastic paralysis of the extremities may occur together with the dementia and in some cases vision fails progressively, resulting finally in blindness.

The prognosis in congenital syphilis of the nervous system is on the whole bad. So many of the cases are those of defective development or malformation of nervous tissue, giving rise to anomalous functions, that we can not expect any improvement. Even in those cases where the symptoms are acquired, if we may use that term, the attack of the virus on the nervous system is usually so severe or has progressed so far before recognition that there is enormous destruction of nerve tissue which can not be replaced.

The treatment does not differ from that of the same symptom-complexes in the adult. The juvenile paresis is just as hopeless, if possible more so—the juvenile tabes has the same prognosis under treatment. Early diagnosis and energetic treatment are the two main points. Psychic disorders in the juvenile form yield but little to treatment. The youth of the patient, beyond a certain point, has proportionately little bearing on the dosage of the spirocheticides employed. It is required that the nervous tissue be sterilized as far as possible and this can not be done by handling the case gingerly.

Before leaving the subject of congenital nervous syphilis it would be well to emphasize the remarks which are made in the chapter on Syphilis of the Nervous System in Adults. They may be applied almost *in toto* to the juvenile form. Any neurologic or psychiatric syndrome occurring in children must be suspected as being of luetic origin. It is true that the profession has abandoned to a large extent the naive attitude towards the so called "upper classes" in regard to syphilis. For this we have the Wassermann reaction to thank. But no supposed impeccability of the parents, no negative previous history of the child and no failure to find Hutchinson's teeth or other stigmata must cause us to eliminate lues from the etiologic possibilities. Complete serologic examinations are imperative and even when they fail us, energetic antispecific therapy will often work wonders.

Congenital Syphilis of the Eye

By Louis S. Greene, M.D., Washington, D. C.

Lesions of the deep structure of the eye are by no means of infrequent occurrence in congenital syphilis of infancy and young children, especially is this the case in diseases of the uveal tract. The iritis is of the plastic type and differs in no essential points from that of the acquired type, save in the time of its appearance, and the fact that the symptoms are usually slightly marked.

It is usually bilateral and generally associated with cyclitis or choroiditis. The time of its appearance is stated by various authors as about the fifth month, although cases occurring during the first month have been reported. Bull reports a case in which he discovered a plastic iritis with synechia, a few hours after birth, proving that the destructive inflammation must have begun *in utero,* and that it was of congenital origin.

According to Weeks, gummous iritis may appear at any time after six months, but seldom after the age of thirty.

Choroiditis is by no means uncommon in infants and young children and, as it presents no external signs, usually it is not discovered until the individual is of sufficient age for the vision to be tested. It presents the same ophthalmoscopic picture as the acquired type and cases are on record where atrophic spots have been discovered in infants a few weeks old, proving, as in cases of iritis, their congenital origin. It is as a rule bilateral, and whereas it may be disseminated, is generally of the anterior variety, hence may easily be overlooked.

Lesions of the retina and optic nerve, like those of the choroid, give no outward signs of their presence, therefore are only recognized when an ophthalmoscopic examination is made, and for this reason, it is indeed essential that infants of parents in whom syphilis is known to exist, should be subjected to a thorough ophthalmoscopic examination at frequent intervals until grown.

With the literature at hand, practically nothing can be found with regard to retinitis in the acute form in infants, the few cases reported revealing this condition in the atrophic stages.

According to Parsons, retinitis is not uncommon in the congenital form. The retina shows a dusty discrete pigmentation

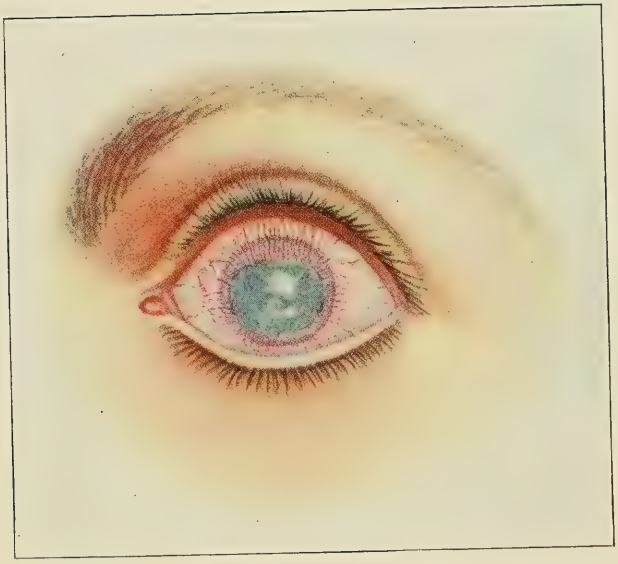

Fig. 140.—Interstitial keratitis.

in the periphery, accompanied by a tigroid condition of the fundus in this situation. However, this is only distinguished by the greater aggregation of pigment from what is often a normal condition.

The optic neuritis of infancy and children is generally associated with a choroiditis. The papilla is indistinct and hyperemic and usually there is no edema of the disc, and in many of these cases atrophy of the optic nerve follows sooner or later.

Paralyses of the extraocular muscles, especially the internal muscles in children, are usually traceable to congenital syphilis. Ingersheimer brings out rather an interesting fact that in twelve cases of nystagmus in young children with negative ophthalmoscopic findings and vision practically normal, the Wassermann reaction was positive in eight cases.

Undoubtedly some forms of congenital cataract are of syphilitic origin, in so much that they may be the result of a syphilitic involvement of the uveal tract *in utero*, therefore, it is essential to search for other stigmata of lues in these cases. Fine dust-like vitreous opacities, especially of the anterior portion, in young children is quite indicative of syphilis due to a preexisting inflammation of the uveal tract, and great care should be taken in searching for other sign of syphilis.

Interstitial keratitis is the most common symptom of congenital syphilis in children between the ages of five to sixteen, although it may appear earlier. It is looked upon as essentially of congenital origin, yet, at times, it is seen in the acquired type. The disease usually begins gradually with slight ciliary congestion followed by the appearance of one or more faint cloudy patches usually near the center of the cornea. Upon examination these are seen to be within the corneal structure. These gradually spread and fuse until the entire cornea becomes lusterless and dull. Blood vessels derived from the ciliary vessels begin to make their appearance in the corneal structure, producing a dull reddish yellow appearance, giving rise to the characteristic salmon patch. After the disease has reached its height, it begins to subside, the cornea clearing from the margin towards the center and finally becomes clear again, except in severe cases.

Iritis is always associated with interstitial keratitis and occasionally choroiditis and retinitis. The disease is bilateral and

whereas the second eye may become involved shortly after the first, yet as much as a year has elapsed before it has made its appearance. The subjective symptoms are diminution of vision, pain, lacrimation, and photophobia.

Various opinions have been advanced as to the true pathology of interstitial keratitis. Parsons considers it an extension forward of a choroiditis, while others claim that the infiltration is due to the direct action of the treponemata, and yet others are of the opinion that it is due to the toxins.

Syphilis of the Ear

By Virginius Dabney, M.D., Washington, D. C.

West's division into three groups of congenital syphilitic disease is a rational method for study, as the clinical features are so different in each of the three, and inasmuch as they occur at such widely different ages. The following is his classification: (1) Cases showing gross aural disease at birth; (2) cases showing aural disease shortly after birth, (3) cases showing aural disease at or after adolescence, or much later (i. e., all cases not included in Classes 1 and 2).

Of the lesions of the external ear, seemingly due to congenital syphilis, I have seen three cases of microtia. Fortunately for society and their own happiness most of the children showing gross syphilitic disease die shortly after birth, but in those less frequent instances where they survive, they become not only deaf mutes, but often mental defectives as well. Of these three the first died at six weeks of age. He showed almost complete absence of pinnæ, and the mastoid process was entirely absent, the face shrunken and prematurely old in appearance. There was a vertical series of fimbriated remnants where nature had intended pinnæ to grow, no canal and apparently no acoustic development at all. The second was a boy of twelve, in whom the left side of the head showed a striking lack of development, which included the pinna, a mere fringe, and no canal. Where the mastoid should have been was a vertical scar, the site of an operation to restore the function of hearing, but the venturesome surgeon desisted when he found no bony canal. The asymmetry extended as far as the parietal bone, the eminence of

which was totally lacking, and the bulge of the frontal bone was also absent. The third case, also unilateral, was that of a man of 35, the general aspects of the case being the same as the second. All three had definite syphilitic histories on the father's side. In such obviously syphilitic cases the diagnosis presents no difficulties, but in the second group we have to depend on other signs of syphilis, such as Hutchinson teeth, which according to Fraser are found in 50 per cent of the cases, a persistent nasal discharge, stubborn middle ear suppuration, interstitial keratitis, defects of the hard and soft palate, or marked deafness without discharge from the middle ear. The stunted appearance, lack of vitality, pallor, and appearance of premature age seen in children from three to six years of age constitute strong presumptive evidence of congenital syphilis. Recourse must be had to the Wassermann test in all doubtful cases, and this is a prudent measure in all cases as it may be highly desirable to have some strong corroborative proof with which to confront parents who are resentful of such a diagnosis without proof, whatever may be their own knowledge of culpability. The hopeless nature of the prognosis in those labyrinthine cases is easily grasped in a perusal of Baratoux's investigations. Of 43 cases reviewed, 19 were stillborn, but of the 24 surviving, 8 had chronic suppurative otitis media, 3 isolated labyrinthine disease, and 8 both middle ear and labyrinthine disease. The labyrinthine cases showed either suppuration therein or hemorrhage and destruction of Corti's organ. The suppuration in this second group may be nonspecific in rare instances, but even so, its course is affected necessarily by the lowered vitality, and rapid destruction of the drum and tympanic contents is apt to ensue, even the internal ear being penetrated by the suppurative process in extreme cases. Rarely condylomata occur (Grueber, Schwartze, Buck, Knapp) and the skin eruption seen on the pinna and in the canal may be in any of its forms (Habermann). I have once seen the macular form, spreading over the pinna and face, in a stillborn infant.

The frequently encountered type of congenital aural disease is that of the adult and late life. According to West the proportion of congenital syphilitics who have deafness and other aural manifestations of syphilis is thus stated by various ob-

servers: Hutchinson and Jackson, 10 per cent; Hermet and Baratoux, 30 per cent (Politzer); Habermann, 20-66 per cent; Alt, 3.1 per cent (labyrinthine deafness); Hinton, 5 per cent (all seen at Guy's Hospital). There is a little closer agreement than this among the authorities as to age limits, eight to eighteen years being the general estimate, or in the neighborhood of fourteen (Knapp).

In the appearance of interstitial keratitis we have presented to us not only a diagnosis of the aural condition impending, or actually active, but a warning as well that treatment started at this time will probably heal in part any aural lesion, but also energetically persisted in will prevent probably those parasyphilitic lesions, which are so destructive to the health and economic value of the patient, even to life itself. The keratitis nearly always precedes by days or weeks the ear lesions, though it may develop simultaneously with it. The estimates as to the preponderance of females over males in congenital syphilitic deafness vary from 2 to 1 (Hutchinson, Gradenigo) to 4 to 1 (Pierce). As the symptoms of adult congenital syphilis of the ear are almost the same as those of acquired labyrinthine syphilis there is no need to repeat them here.

For a further bibliography the chapter upon acquired syphilis of the ear may be consulted.

Diagnosis

The clinical diagnosis of congenital syphilis is usually not difficult to make. In young children several things must be looked for. The history is always important. The parents may give either a history or evident lesions of lues. A history of miscarriages is always of much importance. In the child itself several points must be noted: the general condition is frequently below par, the child may have a wizened appearance and the face may look like that of an old person. There may be rhagades from either the mouth or the anus. An eruption is common. "Snuffles" are frequent, although it must always be borne in mind that rhinitis is frequently found in children who do not have lues. The joints may be painful. Enlarged epitrochlear glands are frequent, and other enlarged glands may occur. The

spleen is enlarged in a high percentage of cases, and the liver is often even larger than usual.

In older children frank gummata may occur. Hutchinson[151] has called special attention to a triad of symptoms, namely, deafness, interstitial keratitis and Hutchinson's teeth. Periosteal lesions should be looked for.

In regard to the laboratory diagnosis but little need be added to the chapter upon general diagnosis in acquired syphilis. It is not always easy to obtain blood for a Wassermann. If it can not be drawn from a vein in the arm either the external jugular or a scalp vein should be tried. These veins always become engorged when the child cries. If the blood can not be obtained directly from a vein either a puncture or a slight incision may be made in the skin and the blood collected from this. The Wassermann is of extreme value in congenital lues, for it is usually positive in the florid stages, although not always in the late stages. Unfortunately most of the articles do not state in what stage of the disease the patient is. Craig[152] states that he has had 82.2 per cent of positive reactions. Holt[153] states that the reaction is practically always positive, and Veeder and Jeans[154] found 92.6 per cent of eighty-two cases positive. Noguchi[155] gives the results of some other observers in his book. It is generally believed that in syphilis hereditaria tarde a positive reaction is the rule, but in view of the fact that in late acquired syphilis the test is not infrequently negative it is extremely probable that this can not always be the case.

The luetin test is often of value, although it is subject to the same limitations as in the acquired form, namely the previous administration of the iodides must be ruled out. Noguchi states that it was positive in 70 per cent of his cases, while Brown[156] reports it positive in 88 per cent.

In newborn children the best way to make the diagnosis is by microscopic examination of the umbilical cord.

Prognosis

It has long been recognized that syphilis is a frequent cause of intrauterine death. Kassowitz[157] states that out of 330 cases only 40 per cent reached term. Still[158] states that in the families of 87 congenital syphilitics there were 39 stillbirths and 36 miscarriages.

Post[159] has studied 168 pregnancies and found that there were 53 stillbirths and miscarriages. Hyde[160] after an elaborate study, found that in seventeen hundred pregnancies there were 579 abortions and stillbirths.

As to the after history of children with congenital syphilis there is a pretty fair agreement in the literature. Osler[161] states that about 75 per cent die. Hyde says that out of 1121 born alive 956 died within the first year. Sturgis[162] reports that in Moscow from 63 to 82 per cent of the affected children succumbed. Still says that out of 87 cases there were 25 cases attributable to congenital lues, and that thirteen more died while under observation. According to Post out of 115 children there were 44 early deaths, and 32 more showed later lesions. Kassowitz reported that 34 per cent die within six months, while Etienne[163] has estimated that 95 per cent die if untreated and 10 per cent if treated.

As regards the individual prognosis there are a number of distinctly bad signs, these are an eruption present at birth, severe pemphigus, jaundice, early nerve lesions and inability to digest food.

Prophylaxis

There are three ways to prevent congenital syphilis, first, to prevent the marriage of syphilitics, second, to prevent conception in a family in which one or both of the partners have the disease, and third, by the intensive treatment of the syphilitic pregnant woman. The first of the points will be covered in the chapter upon Prophylaxis, and the second need not be here discussed. However, the question of the effective treatment of the pregnant must be gone into in some detail. There is considerable literature upon the subject. Jaenselme[164] observed fourteen cases that were treated with arsphenamine and mercury and concludes that the former is superior and that the child will usually go to term and be born alive. Sbilinsky[165] gave arsphenamine to a patient in early pregnancy and two hours later there was hemorrhage with abortion. Auderbert[166] treated seven pregnant women with arsphenamine and most of the children were born healthy and remained so. Two of the cases were confined prematurely. Bar[167] has reported upon six cases which he treated with neoarsphenamine; he was convinced that the drug might be danger-

ous. V'Scilly[168] treated ten patients and found that all gave birth to healthy children. Sauvage[169] has treated 130 women with arsphenamine. He reported that the blood pressure was somewhat raised and felt that this fact should make one cautious in administering the remedy. In 3 out of 84 cases the arsphenamine seemed to hasten the time of birth. Thirty-eight women came to labor at the natural extreme limit, 32 bore their children at the ninth month, two in the eighth, and two in the seventh. The fetal heart sounds became weaker after the administration of the preparation. Of the 91 children, 84 were born living, 77 showed no signs of syphilis after birth, and only 5 were known to have developed syphilis. Pinard, de Ribes, Boissard and Patocki[170] treated 217 cases by mercury or potassium iodide. In 74.54 per cent the children were born dead and in 10 per cent they later developed syphilis. One hundred sixty-three cases were treated with arsphenamine. Over 66 per cent of the children were born alive and without signs of syphilis, 15 per cent showed syphilis soon after birth and the remainder were born well ahead of time and were dead. Other reports quoted by Davis,[171] who has written a very complete article upon the relation of syphilis to obstetrics, show that arsphenamine is much the better drug. In our own hospital work we have never hesitated to give arsphenamine to pregnant women and so far have had no occasion to regret it. Because of the class of patients with whom we have dealt it is impossible to say just what the results have been.

Treatment

Before discussing the treatment of children with congenital syphilis it is well to consider the pathologic condition. In children who show signs of lues soon after birth it must be remembered that the treponemata are already diffused through all of the organs and that they are usually present in great numbers. In other words the condition is similar to that of a well-developed secondary stage of acquired syphilis, except that there are probably more organisms present. In the late stages there are not so many organisms, but the body is in a state of allergy. In other words it is probably impossible to ever produce a radical

cure, such as can often be obtained in the early stages of acquired syphilis.

There have been many men who have tried to treat nursing children through the media of their mothers. However, the results have not been good as Engelmann,[172] Doblin,[174] Baisch,[173] Aschheim[175] and others have pointed out.

It is probably always necessary to treat the child direct with either arsphenamine or mercury. The iodides have no value in killing the treponema, and are upsetting to the digestion, hence are no longer used. Mercury may be given by the mouth, but care must be taken not to disturb the digestion. Either the protiodide or the mercury with chalk may be used. Of the latter we use from ½ to 1 gr. three times a day. One-sixth of a grain of the protiodide a day for a young child is sufficient. The most popular form of administering mercury is by means of the inunctions. The blue ointment, ung. hydrar. fortior, is the old favorite, but personally I prefer a calomel ointment inasmuch as it is so much cleaner, and apparently just as effective. About one dram of either ointment is rubbed over the binder nightly, and the binder then wound around the infant's body. This should be removed daily and the body washed. Intramuscular injections are favored by some, but in general they are irritating and not to be recommended. If one is to use them the best of the soluble salts is certainly the succinimide, employed in doses of $\frac{1}{40}$ of a grain two or three times a week, or the biniodide dissolved in sodium iodide, the dosage being given according to weight, and employed but once a week. Neither of these preparations is especially irritating.

Turning to arsphenamine and neoarsphenamine we find that in the early days a number of deaths were reported from both preparations, and it was thought that the killing of a large number of treponemata and the freeing of their toxins into the circulation might be responsible. Of late we have heard but little of this view. There are two different ways to administer arsphenamine to a newborn child, one by the intravenous and the other by the intramuscular route. The former is often extremely difficult, for suitable veins are hard to find. Either the jugular or the occipital is usually employed and can usually be entered satisfactorily by one who has had a little experience. It is

much better to employ a syringe than the gravity method for such cases. As to dosage we should use about 0.006 gram per kilo of body weight, that is about 0.025 grams for a child of nine pounds. The same size doses may be administered directly into the thigh or gluteal muscles by Sutton's[176] method, and I have often found this extremely useful in the case of children about one year of age. The Hynson, Westcott and Dunning preparation of arsphenamine in cocoa butter has been employed in clinic for the past year with admirable results: this works better than any of the oil preparations that I have ever used. In all cases the child should be wrapped in a sheet so as to prevent struggling.

As regards general treatment the child should always be breast fed, as this gives a much better prognosis. Of course a wet nurse should never be employed unless she be already syphilitic. The children must be kept clean, and must be given every advantage of good hygiene.

Older children with congenital lues must be treated just as are acquired tertiary cases. Treatment must be continued just as in the case of acquired syphilis.

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CHAPTER XXI

DIAGNOSIS

Introduction

When we remember that there are between 6,000,000 and 10,000,000 syphilitics in the United States it is obvious that the diagnosis of this malady is one of importance, both from the public health standpoint and for the good of the patient. At the same time to make a diagnosis of syphilis is a serious affair, and one not to be entered upon rashly. The one rule that I try to impress upon my students is the following: Be quick to suspect syphilis: be slow to diagnose syphilis.

For the correct diagnosis of syphilis we have at our command both clinical and laboratory methods. Unfortunately there is a serious tendency upon the part of the medical profession to ignore the clinical diagnosis and to exploit the laboratory diagnosis, a tendency that is certainly a very dangerous one, for neither laboratory men nor methods are infallible. When one considers the magnificent work that has been done by Jonathan Hutchinson, Fournier and scores of the older syphilographers it can readily be seen that the clinical side should never be ignored. The most valuable of the laboratory methods are the testing of the blood serum for complement fixation, the examination of the spinal fluid, the luetin test, various roentgen ray findings, and last and most important of all, the demonstration of the Treponema pallidum in the lesions.

CLINICAL DIAGNOSIS

History.—The history of the patient should always be carefully taken. While in dispensary work we frequently bluntly ask: "When did you have a sore upon your privates?" and thus at times startle the patient into telling the truth, such a method will not work with the vast majority of private patients. Here we

are forced to use a little diplomacy and to inquire as to certain symptoms, the most important of which are the presence of a generalized, nonitching rash, sore throat, headache especially at night, joint or bone pains, especially tender shins, the history of repeated miscarriages or of children who died shortly after birth. The positive history of a genital sore or of long-standing ulcers is also a matter of considerable importance. The history of falling hair is of but little moment. Naturally the history of the parents, of the children, and of the mate is necessary in many instances.

Physical Examination.—Three classes of patients are seen, those with initial sores, those in early syphilis, and those with late syphilis, either active or latent. The diagnosis of chancre has already been discussed, but it may not be amiss to again call attention to the absolute necessity of examining every genital and every suspicious nongenital sore for the treponema.

As a rule secondary syphilis is easy to diagnose, for there will probably be the remains of a chancre, a well-marked rash, more or less general adenopathy, frequently lesions of the mouth or throat, at times a patchy alopecia, occasionally iritis, and usually some history of headache or more or less well-defined joint or bone pains. Now it should always be remembered that any two or three of these symptoms may be absolutely lacking. The differential diagnosis from other diseases has already been discussed, especially in the chapter upon early cutaneous manifestations. It is at this stage that the Wassermann reaction is of the most value.

Late active syphilis, if the lesions are visible to the eye, is usually easy to recognize, but the various visceral manifestations may require a nice weighing of evidence, especially if the Wassermann be negative. In making a physical examination for syphilis it is well to follow a definite scheme, and the one that we employ is as follows: Search for a scar of a chancre, look for scars upon the skin, especially upon the upper portion of the shins, or for active syphilitic lesions. Go over all of the glands carefully. Examine the eyes, either for an iritis, for changes in the reactions of the pupils, and for paralyses of the eye muscles. Look well at the mouth, hunt for mucous patches, for a glossitis, for a perforation of the palate, or for scars in the neighborhood

of the uvula. If congenital syphilis be suspected examine the teeth thoroughly. Search for nodes upon the long bones, especially the clavicle, tibia, and ribs, also look for an enlarged sternoclavicular articulation, or for nodes upon the bones of the skull, especially the frontal bone. The liver and spleen should always be searched for any enlargement, and the testicles should be examined with care, as gummous deposits in them are common. The condition of the heart and aorta should be investigated as aortitis is far from uncommon in syphilis.

LABORATORY DIAGNOSIS

Demonstration of the Treponema Pallidum.—The causal organisms may be demonstrated in four different ways, first, by the dark-field illuminator, second, by staining secretions from active lesions, third, by an india-ink method, and lastly by staining the organisms in the tissues.

Dark-field Illuminator.—For a satisfactory examination with the dark-field illuminator it is necessary to have clear serum, and but very few blood cells. Usually a chancre is so tender that it can not be squeezed hard enough to exude clear serum. However, if the outer surface be gently cleansed, preferably with a little alcohol, this allowed to dry, and then the surface gently scratched with a knife a little serum will frequently exude: if it does not, suction may be made with a small pipette. If it is still impossible to obtain satisfactory material the lesion should be punctured at the edge: after blood has ceased flowing a little serum will usually exude. In very stubborn cases blood may be collected, allowed to clot, and then the clear serum used. Thompson[1] suggests in extreme cases where clear serum can not be obtained the addition of a drop of 0.1 per cent acetic acid which will lake the blood, but which has the serious disadvantage of destroying the motility of the organisms.

The apparatus consists of the following, a microscope with a good oil immersion lens, and with a rubber funnel diaphragm screwed in just above the lens, a special condenser or dark-field illuminator, which replaces the ordinary substage condenser, a special powerful light, preferably a small arc lamp with a biconvex lens, and thin slides and cover-slips. The light is focused by

means of the usual mirror on the microscope. The dark-field is so constructed that the direct rays of light are cut out by an opaque stop, while the peripheral rays are reflected from the sides of the instrument and are focused at a spot which will strike the top of a glass slide, laid on the instrument. This illuminates all objects brilliantly against a dark background. A drop of immersion oil must be placed upon the dark-field and the slide pressed against this, then oil is also placed on the upper surface of the cover-slip just as in other oil immersion work.

The dark-field has several great advantages: in the vast majority of instances it will enable an absolute and early diagnosis of

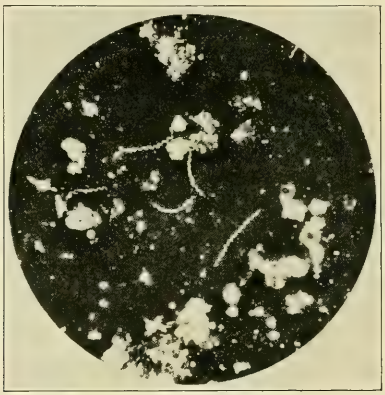

Fig. 141.—The Treponema pallidum can be best recognized by the dark-field illuminator. (Courtesy of the E. Leitz Co.)

syphilis to be made within a very few minutes. It must always be borne in mind that if a lesion has been treated with antiseptics so many of the treponemata may have been killed that they can not be demonstrated: in such instances it may be necessary to prevent the patient from using local applications for a day or two and then reexamine. In the second place this instrument affords much the best chance of showing the organisms, for if they are in the serum they can not be missed, provided that the observer is a trained one. It must always be remembered that in the mouth there are treponemata that closely resemble the organism of syphilis, and as a result the findings of apparent treponemata from mouth lesions must be interpreted with the

greatest reserve. Personally I never attempt to use the dark-field for the diagnosis of mouth lesions, unless I suspect a chancre, and then I take care to secure serum from deep in the growth.

India-ink Method.—This method was originally described by Burri for the demonstration of bacteria against a dark background, depending for its value upon the fact that bacteria, spirochetes, etc., are not stained, while the serum in which these organisms are found becomes a dark brown color. The technic is simple, a drop of serum is placed upon a glass slide, and to this is added a drop of Günther-Wagner's waterproof ink that has been well centrifugalized, or mixed with tincture of iodine in the proportion of one part iodine to 600 of ink as suggested by Frost. There are two objections to this method, one, that the organisms do not show motility, and second, as pointed out by Walters, that many of the inks show spiral organisms that resemble the treponema. Walters[3] recommends rubbing up a bit of a dry stick of India ink in a mortar with some sterile distilled water.

Collargol Method.—The use of collargol as a substitute for India ink has been recommended by various writers, and the directions usually given are to add one part of the powdered collargol to nineteen parts of distilled water. As a matter of fact the dark field illuminator should totally displace both of these methods.

Stained Smear Method.—A number of years ago it was the vogue to search for the organism in stained smears, and numbers of stains have been devised. Careful comparison with the dark-field method has conclusively shown that it is frequently possible to demonstrate organisms by this method when stained films fail to reveal their presence, hence it should be discarded. One of the best known stains is the Giemsa which is made as follows:

Azure II	8 grams.
Azure II eosin	3 grams.
Glycerin, C. P.	250 grams.
Methyl alcohol (Kahlbaum)	250 grams.

This stain may be purchased from almost any dealer in laboratory supplies, and is used as follows: one drop of stain is added to one cm. of distilled water, and to this is added one drop of a 1:1000 solution of potassium carbonate. The film to be stained must be upon a perfectly clean slide or cover-slip and must be

very thin. The films are dried in the air, fixed in absolute alcohol for fifteen minutes and stained for at least forty-five minutes, then washed with distilled water, blotted, and if on coverslips, mounted with Canada balsam.

The Goldhorn stain is more rapid, but is difficult to manufacture. Thompson states that it should be made as follows: Dissolve 1 gram of lithium carbonate in 200 c.c. of distilled water. Add 2 grams of methylene blue, heat carefully, filter, and divide into two parts. Add 5 per cent acetic acid to one part until it is acid to litmus, and then mix with the other part. After this add a weak solution of eosin until a pale blue color is obtained. Let stand for twenty-four hours and then filter off the precipitate which forms, and dry without heat. Dissolve 1 gram of powder in 100 c.c. of absolute methyl alcohol. The smears are fixed for fifteen minutes in absolute methyl alcohol and are then stained for ten minutes.

Practically any of the Romanowsky stains will frequently demonstrate the organism, either Wright's, Hasting's or Jenner's modification may be employed. The stain should act for about fifteen minutes instead of the usual time.

For staining the organism in tissues the Levaditi method is almost universally employed. The principle of the stain is that the tissues are stained in block and that the organisms become impregnated with a silver salt. Various modifications of this method have been suggested, but the one that Levaditi recommends is the following:

1. Place a small bit of tissue in 4 per cent formaldehyde for twenty-four hours.

2. Dehydrate in 95 per cent alcohol for twenty-four hours.

3. Wash in distilled water until tissue sinks to bottom.

4. Put tissue in a stoppered bottle which contains a 1 per cent solution of silver nitrate to which has just been added 10 per cent of pyridin. Allow to remain at room temperature for three hours and then incubate at 50° C. for six hours.

5. Wash in a 10 per cent solution of pyridin.

6. Place in a bottle which contains a 4 per cent solution of pyrogallic acid, to which has just been added 10 per cent of pure

acetone and 15 per cent of the total volume of pyridin. Allow to remain for three hours.

7. Dehydrate in graded alcohols, beginning with 30 per cent and finishing with absolute, allowing the tissue to remain for three hours in each.

8. Clear in xylol until the tissue sinks.

9. Immerse in melted paraffin at 52° C., giving three changes and allowing one-half hour for each.

10. Block in paraffin and cool by immersion in cold water.

11. Section, cutting from five to ten microns.

12. Attach to slide, preferably with Mayer's mixture which consists of equal parts of egg white and glycerine, beaten and filtered with the addition of a small amount of phenol.

13. Heat over Bunsen burner sufficient to melt paraffin.

14. Place in xylol for a few moments.

15. Mount with Canada balsam.

By many pathologists the original Levaditi method is preferred. This is as follows:

1. Fix tissue in 10 per cent solution of formalin for twenty-four hours.

2. Wash in water.

3. Dehydrate in 95 per cent alcohol for twenty-four hours.

4. Wash in distilled water until tissue sinks to the bottom.

5. Impregnate in a 2 per cent solution of silver nitrate for three to five days in the dark at a temperature of 38° C.

6. Wash in water and reduce overnight in the following bath: pyrogallic acid 4 grams, formalin 5 c.c., distilled water 91 c.c.

7. Wash in water, dehydrate, and imbed in paraffin in the usual way.

8. Cut and mount sections in balsam.

The Wassermann Test in the Diagnosis of Syphilis

By Charles F. Craig, M.D., Colonel, Medical Corps, U. S. Army

It is now over ten years since Wassermann, Neisser, and Bruck[4] published their description of what is generally known as the Wassermann test, and during this time it may be stated that no diagnostic measure ever devised has received a more thorough trial or been subjected to a more searching analysis.

At the present time, the general consensus of opinion is that, all in all, this test is the most valuable aid that we possess in the diagnosis of syphilis, and although many unfortunate mistakes have occurred in the interpretation of the results of the reaction, due to carelessness or inexperience on the part of those performing the test, the fact remains that in this reaction we have what is probably the most valuable and generally useful measure known to the practitioner of medicine.

In order to thoroughly understand what follows in regard to the Wassermann test and its application, it is absolutely necessary that the terms which are generally used in describing the reaction be clearly understood, for if the meaning of these terms is once mastered, the theory and technic of the test are easily comprehended.

The complement-fixation test for syphilis, or the Wassermann test, as it is usually called, is the direct result of Bordet's discovery of the principle of complement fixation, and the same terms are employed in describing this reaction as in describing complement fixation in general. Just as in complement fixation a *bacteriolytic* and *hemolytic* system are employed in making the test, so in the Wassermann test we use what answers to a bacteriolytic system and, also, a hemolytic system.

A *bacteriolytic system* consists of *antigen, amboceptor,* and *complement,* while a *hemolytic* system consists of the same elements. In a *bacteriolytic* system the *antigen* consists of an emulsion of a specific bacterium; the *amboceptor,* of the blood serum of an animal immunized against the bacterium used in the antigen; and the *complement* is the fresh blood serum of some animal, guinea pigs being generally used for the purpose. In a *hemolytic* system the *antigen* consists of a suspension of red blood corpuscles from an animal; the *amboceptor,* of the blood serum of an animal immunized against the specific red blood corpuscles used in the antigen; and the *complement* of the fresh blood serum of guinea pigs or other animals.

When the three elements of a bacteriolytic system are mixed together and incubated for a certain time, the end result is the dissolving of the bacterium in the mixture and is known as *bacteriolysis,* while if the three elements of a hemolytic system

be added together, the end result is the dissolving of the red blood corpuscles in the mixture, and the process is known as *hemolysis.* That either bacteriolysis or hemolysis occur it is absolutely necessary that fresh serum or complement be present in the mixture, for if this is not present the exposure of a specific antigen to a specific amboceptor is followed by a negative result so far as any effect upon the specific antigen is concerned. In the same way, the antigen must be a specific one for the immune serum, or amboceptor employed, or no reaction occurs. Thus the blood serum of an animal immunized against typhoid fever will, in the presence of complement, dissolve the typhoid bacilli, or antigen, but it will not act upon any other bacterium.

An *antigen* may be defined as any substance, which, when injected into an animal, gives rise to antibodies or amboceptors.

An *amboceptor* is an antibody produced by the injection into an animal of an antigen.

Complement is contained in any fresh blood serum.

In practice the term "antigen" is employed for the emulsion or suspension containing the specific antigen; the term amboceptor for the serum containing the antibody; and the term complement for the fresh blood serum employed in making tests.

As I have already stated, the Wassermann test for syphilis is based upon the well-known phenomenon of complement fixation, discovered by Bordet and Gengou.[5] These investigators proved that it is possible to fix or bind complement when it is added to a specific antigen and amboceptor and that by utilizing this phenomenon it was possible to devise a test which will demonstrate the presence of a specific antigen or amboceptor in a properly prepared solution, and to this test they gave the name of complement fixation. Thus, if a suspension of typhoid bacilli, i.e., typhoid antigen, be added to the diluted blood serum of a typhoid patient, which contains the antibody or amboceptor to the typhoid bacillus, and complement, or fresh guinea pig serum be added to this mixture, the complement is fixed or bound, so that if later we add to this mixture a suspension of red blood corpuscles and serum containing amboceptor for these red blood corpuscles, no hemolysis occurs,

because the complement, without which hemolysis is impossible, has already been used up or fixed in the reaction between the typhoid antigen and antibody. Thus, the absence of hemolysis proves that typhoid fever exists in the patient, or the complement would not have been bound, and the reaction is called a positive one. On the other hand, if typhoid fever were not present, the patient's blood serum would not have contained the typhoid antibody or amboceptor, and no reaction between the patient's serum and the antigen could occur, and consequently the complement is not used up and when later the red blood corpuscles and the antibody against them are added, hemolysis results and the reaction is called a negative one, as it demonstrates that the patient's serum does not contain the antibody or amboceptor against the typhoid bacillus.

Basing their work upon this phenomenon of complement fixation, Wassermann and Bruck endeavored to make use of it in the diagnosis of tuberculosis, using as antigen aqueous extracts of tuberculous lungs, but, although they met with some measure of success, the results were not sufficiently encouraging, at that time, to warrant the practical use of this test in the diagnosis of this disease.

While they were conducting their researches upon tuberculosis the trepanema of syphilis was discovered, and this led them, in conjunction with Neisser, to try complement fixation in the diagnosis of syphilis. Their work resulted in the publication of the technic of the Wassermann test, and a few days after the publication of the paper by Wassermann, Neisser, and Bruck, a paper on the same subject appeared by Detre,[6] who independently arrived at the same conclusions as the authors mentioned, so that the test might well be known as the Wassermann-Detre reaction or test.

Until 1907, the Wassermann reaction was considered a true antigen-antibody reaction, but observations by several investigators have since shown that it can no longer be so considered, as the use of nonspecific substances as antigen are as valuable in practice as the use of substances containing the trepanema causing the disease. In 1907 Weygandt[7] obtained a positive reaction in tabes by using an antigen prepared by extracting a normal spleen, and Marie and Levaditi[8] obtained

positive reactions in paresis with an aqueous extract of normal liver. Later, Plaut,[2] Landsteiner,[3] and others, obtained positive results in syphilitics with aqueous extracts of normal organs, both of animals and man, and finally, the publication of the paper by Landsteiner, Muller, and Potzl,[3a] in which they showed that as good results could be obtained in the diagnosis of syphilis with this test by using as antigen alcoholic extracts of guinea pig heart as when aqueous extracts of fetal syphilitic liver were used for this purpose, definitely decided the question of the nonspecificity of the test from the standpoint of a true antigen-antibody reaction. The work of these investigators was quickly followed by that of many others and it was found that a variety of substances could be used as antigen in the Wassermann test, among the best known and most reliable being cholesterinized alcoholic extracts of normal human heart muscle and Noguchi's acetone insoluble fraction of normal organs.

As will be noted later, while the Wassermann reaction, as shown by the investigations mentioned, can no longer be regarded as a true antigen-antibody reaction and therefore, as a specific reaction, in the true sense of that term, the practical application of the test in hundreds of thousands of instances has proved that, with the exception of a few easily recognized conditions, the test is specific of syphilis and the margin of error so slight as to be negligible in practice, if the test be properly performed.

Nature of the Reaction.—The exact nature of the Wassermann reaction is still a mystery despite the immense amount of research that has been expended in trying to solve this problem. The discovery that the antigen to be employed in the test need not be a specific one introduced an element of confusion into the question, and induced many physicians, for a time, to look with suspicion upon the reaction and refuse to use it in their practice. However, the combined experience of numerous investigators has proved that while it is true nonspecific substances act as antigens when employed in the test, the real value of the measure as a diagnostic method is in no way injured by reason of this fact.

As generally performed the test appears to consist in a reaction between lipoids present in the antigens used and lipotropic substances present in the blood serum of syphilitics, but, on the other hand, it has been amply demonstrated that a true antigen-antibody reaction may be obtained with the blood serum of certain syphilitics, when specific antigens, prepared from cultures of treponema pallidum are employed in the test. However, the employment of these specific antigens in practice has proved a failure, due to the fact that only a small proportion of syphilitics react when such antigens are used, and because the reaction is in the nature of a group reaction. This latter point was first proved by Nichols and myself,[11] in 1912, for we found that alcoholic extracts of pure cultures of *Treponema pallidum, Spirochaeta pertenuis, Spirochaeta microdentia* and *Spirochaeta refringens* gave complement fixation with syphilitic serum, while antigens made from *Bacillus typhosus* and *Spirillum cholerae* gave negative results. Our findings have since been confirmed by Kolmer, Williams and Laubaugh[12] and others, but the specific pallidum antigen can not be used in practice owing to its unreliability, as has been already stated.

The fact that a specific complement fixation reaction, within the limits of a group, can be obtained with an antigen prepared from cultures of Treponema pallidum, renders it probable that an antigen prepared from a fetal liver rich in organisms might give positive reactions where the nonspecific antigens were negative, so that such an antigen should approach nearer the ideal than one prepared from normal tissues. The reaction, when such an antigen is used, is probably of a dual nature, consisting, in some instances, of a true antigen-antibody reaction and a nonspecific reaction between the lipoids in the antigen and lipotropic substances in the patient's serum.

Other theories have been advanced to explain the reaction, but it may be stated that at the present time all that we know regarding the phenomenon is that the reaction depends upon lipoids and lipotropic bodies, or as Kolmer well says, is intimately concerned with the chemistry of the lipoids, for, while there is undoubtedly, in some cases, a true antibody reaction between specific substances in the antigen prepared from treponemata and bodies in the patient's serum, the vast majority

of the positive reactions are due to the presence of substances in the blood serum or from the tissues which have been either influenced or produced by the activities of the treponemata which are the etiologic factor in the disease.

The Materials Used in the Test and Their Preparation.—In describing the preparation of the materials to be used in making the Wassermann test I shall describe them as they are used in making the test in the army laboratories, touching upon other methods when describing various modifications of the test employed by others.

The test as generally performed in the army, following the technic originally worked out by me, consists of a modification of the Wassermann reaction by using a human hemolytic system and in reducing the quantities of serum tested, as well as by employing not only an antigen prepared from a human fetal syphilitic liver but also using cholesterinized antigens The following reagents are used in making the test:

1. **Complement.**—The fresh blood serum of guinea pigs.
2. **Amboceptor.**—The serum of rabbits immunized to human erythrocytes.
3. **Antigens.**—An alcoholic extract of fetal syphilitic liver, and cholesterinized extracts of human heart.
4. **Blood Corpuscle Suspension.**—A five-tenths of one per cent suspension of human red blood corpuscles in normal salt solution.
5. **Patient's Blood Serum,** inactivated at 56° C. for one-half hour.

Preparation and Titration of Complement.—The complement consists of the blood serum of guinea pigs. As pigs vary considerably in the strength of complement in their serum it is always best to use the serum from at least two pigs. If a few tests only are to be made the pig may be bled from the heart, a puncture into the organ being made with a hypodermic needle attached to a glass syringe holding 10 c.c. and almost this amount may be drawn from a large pig by this method without danger. After removal, the blood is ejected into a sterile Petri dish, allowed to stand at room temperature for an hour and then placed in the ice box overnight. In the morning the clear serum should be pipetted off and diluted with an equal amount of salt solution (.85 per cent).

If a great many tests are to be made it is better to sacrifice the pigs by cutting their throats, each animal being held over a Petri dish, the throat cut with a sharp knife or razor, and the blood allowed to run into the dish. Great care should be taken not to cut through into the esophagus, for if the secretions of the stomach become mixed with the blood the serum loses part or, in some instances, all of its complementary power. The syringe, needle, Petri dishes and all other apparatus used in collecting the blood

from the guinea pigs should be sterile and perfectly dry, although the syringe may be washed out with salt solution prior to use.

After pipetting off the serum from the clot it should be diluted with an equal amount of 0.85 per cent salt solution and this constitutes the complement solution as used in the test. It should not be blood stained and no red blood corpuscles should be present. If they are the mixture should be centrifuged and the blood corpuscles thus removed.

As this mixture of complement and salt solution varies greatly in strength at various times it is absolutely essential that it be titrated each day before it is used. It can be kept in an ice box for three to four days but usually upon the fourth day the titration will demonstrate that it is so weak as to be practically useless. The complement is at its best about thirty-six hours after withdrawal from the pig but is much weaker immediately after withdrawal and grows gradually weaker from day to day. Attempts have been made to preserve the complement by the addition of various substances but none of the methods recommended have come into general use.

Titration of the Complement.—As stated, the complement should be carefully titrated each day before it is used. If this is not done grave errors will result in the test and cases that should be positive may be rendered negative, or, what is more common, negative cases will give a false positive result. After the complement has been diluted as mentioned above, varying amounts are tested as shown in the Table I, ten tubes being employed in the titration.

TABLE I

TITRATION OF COMPLEMENT

TUBE NO.	AMOUNT OF SALT SOLUTION	AMOUNT OF BLOOD SUSPENSION 5 PER CENT	AMOUNT OF AMBOCEPTOR	AMOUNT OF COMPLEMENT	Incubate in water-bath at 37° C, for one hour and then read result.
	C.C.	C.C.	Unit	C.C.	
1	0.9	0.1	2	0.02	
2	0.9	0.1	2	0.03	
3	0.9	0.1	2	0.04	
4	0.9	0.1	2	0.05	
5	0.9	0.1	2	0.06	
6	0.9	0.1	2	0.07	
7	0.9	0.1	2	0.08	
8	0.9	0.1	2	0.09	
9	0.9	0.1	2	0.10	
10	0.9	0.1	0	0.10	

After incubating in the water-bath at 37° C. for one hour or in an incubator at the same temperature for two hours, the smallest amount of complement that has caused complete hemolysis is noted and this is called one unit of complement. For example, if it is found that Tube No. 4, containing 0.05 c.c. of complement is the first of the tubes to show com-

plete hemolysis, the tubes preceding it being only partially hemolyzed, then 0.05 c.c. of the diluted serum, or complement, constitutes one complement unit, and in performing the Wassermann test twice this amount, or 0.1 c.c. of the complement is used for each tube employed in the test. The control tube, No. 7, which contains no complement, should show no hemolysis.

Preparation and Titration of Hemolytic Amboceptor.—The hemolytic serum or amboceptor used in the Wassermann test, as performed by me, is prepared by immunizing rabbits to human red blood corpuscles. The human hemolytic system has been adopted because it is believed that it gives the most accurate results with human blood serum, and because by using it, the natural antisheep amboceptor normally present in human blood, and which interferes markedly with the accuracy of the test when the sheep hemolytic system is employed, is thus avoided. The only objection that can be urged against the human hemolytic system is that it is slightly more difficult to immunize rabbits to human red corpuscles than it is to sheep corpuscles, and that it requires more careful technic both in collecting the blood and in injecting it into the animals, but this objection is of no practical importance when the advantages of the human system are considered.

Well grown, healthy rabbits are selected and given repeated injections of washed human erythrocytes. The number of injections and their location vary with different workers but I have found that the most rapid method of immunizing the animals, and securing a good hemolytic serum, is to give an intravenous injection, in the ear vein, of 1 c.c. of washed corpuscles every other day until five injections are given when the rabbit's serum should be titrated and will generally be found to be strong enough in hemolytic properties to be used for the test. By this method it is seldom that an animal is lost, as the frequent injections prevent the development of anaphylactic phenomena, and a good amboceptor serum may be obtained in a comparatively short time.

Another good method is to give one subcutaneous injection in the skin of the abdomen of 5 c.c. of the washed erythrocytes and followed by from two to four intravenous injections in the marginal ear vein, of 3 to 4 c.c. of washed erythrocytes, at intervals of from five to six days. This method often gives excellent results, but it is slower and it is not uncommon to lose an animal from anaphylaxis during the process. All in all, the method first mentioned will be found most satisfactory. Whichever method is used the rabbit's blood serum should not be tested for its hemolytic strength until from 7 to 9 days have elapsed from the date of the last injection of erythrocytes.

The blood corpuscles are prepared for injections as follows: The requisite amount of blood (allowing at least twice the amount of blood for the amount of corpuscles to be used in the injection) is withdrawn from one of the large veins of the arm with a glass syringe, which has been sterilized and washed out with sodium citrate solution. After drawing the blood it is at once mixed with from 200 to 250 c.c. of normal salt solution in a flask and distributed into centrifuge tubes and centrifuged until the erythro-

cytes are collected at the bottom of the tubes. The supernatant salt solution is now carefully poured or pipetted off and the tubes again filled with fresh salt solution, well shaken, and again centrifuged. This process is repeated for four times, when the supernatant salt solution is tested for albumin and if a trace of the latter is found the washing is again repeated and continued until no reaction for albumin is obtained. Almost invariably four washings will be found sufficient.

After the corpuscles are washed they are mixed with as little salt solution as possible and at once injected either subcutaneously or intravenously with a sterilized syringe. From 7 to 9 days after the fifth intravenous injection, if the first method of immunization has been followed, or after the third, or fourth injection, if the second method has been chosen, the rabbit should be bled from the marginal ear vein into a Wright capsule, from 1 to 2 c.c. of blood being collected and the serum titrated to determine its hemolytic strength. If it is not found strong enough, the injections are resumed and it will generally be found that one or two more will render the serum strong enough for use in the test.

The preliminary titration may be easily done in the following simple manner: A small amount of the rabbit serum is allowed to flow into a capillary pipette and one drop from the pipette is mixed with 39 drops of normal salt solution from the same pipette, thus giving a dilution of the serum of 1-40. The titration of the amboceptor serum thus diluted is shown in Table II. The serum should be inactivated by heating for one-half hour at 56° C. before it is diluted and titrated.

Table II

Preliminary Titration of Amboceptor Serum

TUBE NO.	AMOUNT OF SALT SOLUTION C.C.	AMOUNT OF COMPLEMENT, UNITS	AMOUNT OF BLOOD SUSPENSION 5% C.C.	AMOUNT OF AMBOCEPTOR, 1-40 DROPS	Incubate in water-bath at 37° C. for one hour.
1	0.9	1*	0.1	1	
2	0.9	1	0.1	2	
3	0.9	1	0.1	3	
4	0.9	1	0.1	4	
5	0.9	1	0.1	5	
6	0.9	1	0.1	None	

*If the unit of complement has not been determined by a previous titration, use 0.05 c.c. of a 1-2 dilution, as this is generally the unit determined by titration.

After incubating in the water-bath at 37° C. for one hour, or in an incubator at the same temperature, for two hours, the titration is read, and if either tube containing one or two drops of the rabbit serum is completely hemolyzed, the serum is strong enough for practical purposes and the rabbit should be bled. Bleeding is done by cutting the carotid vessels while holding the animal over a large glass dish, into which the blood is allowed to flow. The dish is then set aside for an hour at room temperature

and then placed in the ice box and allowed to remain overnight. In the morning the clear serum is pipetted off into small test tubes, inactivated by heating in a water-bath at 56° C. for one-half hour and then kept in the ice box, or suitable filter paper is impregnated with the serum.

In this laboratory the amboceptor serum is invariably preserved by impregnating filter paper because I have found that the serum keeps much better and for a longer time when preserved in this way and there is no danger of infection. The method of preparing amboceptor paper is as follows: The filter paper used for the purpose is Schleich and Schull's, No. 597, cut into squares measuring 10 by 10 cm. It has been determined that it takes about 1.5 c.c. of the rabbit serum to saturate one square of this paper, so that the number of squares needed can be easily calculated from the amount of serum available. This number is placed, one by one, in a Petri dish containing the serum and the process continued until all the serum is absorbed by the paper. The slips of paper are then lifted with a pair of forceps, thoroughly drained, drawn carefully across the edge of the dish a few times to remove the excess of serum, and then placed upon a sheet of unbleached muslin, which should be large enough to contain all the pieces of paper that have been saturated. The muslin containing the paper is then placed under an electric fan and the paper rapidly dried, after which it is placed in an air-tight glass jar and kept at room temperature in a dark place. The amboceptor paper thus prepared will keep for many months with very little loss of strength, although it is well to titrate it at least once a month. I have repeatedly used amboceptor paper a year old in practically the same dose as when it was first made but it is always wise to titrate it at intervals of a month.

The *titration of the amboceptor paper* is necessary in order to ascertain the amount that should be used in making the Wassermann test and is done in the following manner:

Titration of Amboceptor Paper.—After being thoroughly dried, a strip of the amboceptor paper measuring 5 mm. wide is cut from one of the sheets and varying lengths of this used in the titration, according to the scheme shown in Table III.

TABLE III

TITRATION OF AMBOCEPTOR PAPER

TUBE NO.	AMOUNT OF SALT SOLUTION C.C.	AMOUNT OF COMPLEMENT UNIT	AMOUNT OF BLOOD SUSPENSION, 5% C.C.	AMOUNT OF AMBOCEPTOR PAPER, MM.	Incubate in water-bath at 37° C. for one hour.
1	0.9	1	0.1	5 by 1	
2	0.9	1	0.1	5 by 2	
3	0.9	1	0.1	5 by 3	
4	0.9	1	0.1	5 by 4	
5	0.9	1	0.1	5 by 5	
6	0.9	1	0.1	None	

*If the unit of complement has not been determined by titration against a known sample of amboceptor paper, use 0.05 c.c. of a 1-2 dilution of the complement.

After incubating in the water-bath for one hour, the tubes containing the paper being shaken every fifteen minutes, or in an incubator for two hours, the titration is read and the first tube showing complete hemolysis is noted and that amount of the paper is called one unit of amboceptor. A good amboceptor paper should show complete hemolysis in tubes 2 or 3, or with pieces of paper measuring 5 by 2 or 3 mm. In making the test two units of the amboceptor paper should be used. The control tube, No. 6, should not show any hemolysis.

Before impregnating the filter paper with the amboceptor serum it is necessary, of course, that the serum be inactivated at 56° C. for one-half hour, in the water-bath, in order to get rid of complement.

Preparation and Titration of the Antigen.—As I have already stated a great many substances have been used as antigen in the Wassermann test but in the army we have found that alcoholic extracts of fetal syphilitic liver and cholesterinized alcoholic extracts of normal heart muscle have given the most satisfaction and the preparation of these will here be described. The acetone insoluble lipoid antigen of Noguchi is also used at times in conjunction with the other antigens mentioned and is especially valuable in treated cases.

Preparation of Alcoholic Extract of Syphilitic Liver.—A fetal liver rich in treponemata is selected, washed free from blood, and any fat present is removed. One hundred grams is weighed out, all blood removed by thorough washing, and cut into very small pieces or run through a meat grinder. The material is then placed in a large bottle and 1000 grams of absolute alcohol added and the whole is then placed in an incubator at 37° C. for ten days, being thoroughly shaken three times a day. If a shaking machine is available the material is placed in suitable bottle and shaken for 24 hours, at the end of which time it is thoroughly extracted. After extraction is completed the material is filtered through filter paper and the filtrate evaporated to two-thirds its original volume, when it is ready to titrate.

Preparation of Cholesterinized Heart Extract.—The same method is used in preparing alcoholic extract of human heart muscle, the material being washed free from blood, all fat removed, and 100 grams of the heart muscle being cut into small pieces or run through a meat grinder and extracted with absolute alcohol in the same proportions. After extraction the material is filtered, evaporated to two-thirds its volume, filtered through filter paper, and 0.4 per cent of cholesterin added. This generally gives a saturated solution as cholesterin is very slightly soluble in alcoholic solutions. After the addition of the cholesterin the antigen is bottled and kept in an ice box. It is very essential that all antigens be kept cold as they rapidly lose strength if kept at room temperature.

Preparation of Noguchi's Acetone-insoluble Lipoid Antigen.—As this antigen is often used either alone or in conjunction with the antigen described, by many workers, a brief description is here included of its preparations.

Normal organs are used for this antigen and may be obtained either from

man or the lower animals. Extracts made from human heart muscle, liver, or kidney or from the same organs of guinea pigs or rabbits are satisfactory and the extraction is done in the same manner as for the antigens already described, 10 parts of absolute alcohol being used for each part of the organ. After extraction, the material is filtered and the filtrate evaporated to dryness by the aid of an electric fan. The residue is then taken up with ether and the solution thus obtained allowed to stand overnight in a cool place. In the morning the supernatant ether will be found perfectly clear while the insoluble portion has settled to the bottom of the receptacle. The clear ethereal portion is decanted off and evaporated to a small quantity, and mixed with ten volumes of pure acetone. The precipitate which forms is allowed to settle and the supernatant liquid poured off. The precipitate is light brown in color and forms the material from which the antigen suspension is made, 0.3 gram of this acetone-insoluble fraction being dissolved in 1 c.c. of ether and then mixed with 9 c.c. of methyl alcohol. This mixture may be kept for a long time and the antigen suspension used in making the test is prepared by adding 1 c.c. of this stock solution to 9 c.c. of normal salt solution.

Titration of Antigen.—The antigenic extract must be titrated with a known syphilitic serum in order to test its antigenic qualities; a normal serum in order to demonstrate that it will not inhibit hemolysis when such a serum is present; and also without either a normal or syphilitic serum in order to show that it is neither hemolytic nor inhibitory of itself. Before titration the antigenic extract should be properly diluted, which is done by adding one part of the extract to 9 parts of normal salt solution. Any antigenic extract prepared in the manner described and diluted so as to produce an emulsion containing one part of the extract to 9 parts of normal saline, that is neither hemolytic nor inhibitory of itself or in the presence of a normal serum in a dose of 0.2 c.c. and that gives complete inhibition of hemolysis in the presence of a syphilitic serum in a dose of 0.05 or 0.1 c.c. will be found to give satisfactory results in practice.

The accompanying tables illustrate how the necessary titrations of the antigen are performed, the quantities of antigenic emulsion tested having been determined by a large number of experimental tests to yield satisfactory practical results.

TABLE IV

TITRATION OF ANTIGEN FOR HEMOLYTIC PROPERTIES

TUBE NO.	AMOUNT OF SALT SOLUTION C.C.	UNITS OF COMPLEMENT	AMOUNT OF ANTIGEN EMULSION C.C.	AMOUNT OF BLOOD SUSPENSION 5% C.C.	Incubate in water-bath at 37° C. for one hour.
1	0.9	2	0.05	0.1	
2	0.9	2	0.10	0.1	
3	0.9	2	0.15	0.1	
4	0.9	2	0.20	0.1	
5	0.9	2	None	0.1	

In the above titration none of the tubes should show hemolysis. If hemolysis should be present in all, including Tube No. 5, the control tube without antigen, it would indicate that hemolytic substances were present in the complement or the blood suspension, or both. However, if hemolysis occurs in only one or more of the tubes containing antigen, the control remaining unhemolyzed, it demonstrates that the antigen is hemolytic, and, in this event, it should be discarded. If none of the tubes containing antigen show hemolysis the antigen is not hemolytic and, therefore, so far as hemolysis is concerned, safe to use in making the Wassermann test.

The method of titrating the antigenic emulsion in order to determine its anticomplementary properties is shown in Table V.

TABLE V

TITRATION OF ANTIGEN FOR ANTICOMPLEMENTARY PROPERTIES

TUBE NO.	AMOUNT OF SALT SOLUTION C.C.	UNITS OF COMPLEMENT	AMOUNT OF ANTIGENIC EMULSION C.C.	AMOUNT OF BLOOD SUSPENSION 5% C.C.	UNITS OF AMBOCEPTOR PAPER	Incubate in water-bath for one hour at 37°C.
1	0.9	2	0.05	0.1	2	
2	0.9	2	0.10	0.1	2	
3	0.9	2	0.15	0.1	2	
4	0.9	2	0.20	0.1	2	
5	0.9	2	None	0.1	2	

As the result of this titration there should be complete hemolysis in all of the tubes. If the control tube, No. 5, should show inhibition of hemolysis, it would demonstrate that either the complement, amboceptor, or blood suspension was untrustworthy but if any of the tubes containing the antigen emulsion show inhibition of hemolysis it demonstrates that the anti-

TABLE VI

TITRATION OF ANTIGEN TO DETERMINE ANTIGENIC PROPERTIES

TUBE NO.	AMOUNT OF SALT SOLUTION. C.C.	AMOUNT OF SYPHILITIC SERUM INACTIVATED C.C.	UNITS OF COMPLEMENT	AMT. OF ANTIGENIC EMULSION C.C.	Incubate in water-bath at 37° C. for 30 minutes.	AMOUNT OF BLOOD SUSPENSION 5%. C.C.	UNITS OF AMBOCEPTOR	Incubate in water-bath for one hour at 37° C.
1	0.9	0.1	2	0.05		0.1	2	
2	0.9	0.1	2	0.10		0.1	2	
3	0.9	0.1	2	0.15		0.1	2	
4	0.9	0.1	2	0.20		0.1	2	
5	0.9	0.1	2	None		0.1	2	
6	0.9	Normal serum. 0.1	2	0.10		0.1	2	
7	0.9	Normal serum. 0.1	2	0.20		0.1	2	
8	0.9	Normal serum. 0.1	2	None		0.1	2	

gen is anticomplementary, and under such circumstances it should be discarded.

Having tested the antigen for its hemolytic and anticomplementary properties it is now necessary to test it with a known positive serum to determine its antigenic qualities and also with a known normal serum, in order to demonstrate that it will not give positive results with nonsyphilitic sera. This titration is made as shown in the following table:

As a result of this titration all of the tubes containing antigen and syphilitic serum should show *absolute inhibition of hemolysis.* Control Tube 6, containing normal serum, and control tube 7, also containing normal serum, should show complete hemolysis, while control tube 8, containing normal serum and no antigen should also show complete hemolysis. Control Tube 5, containing syphilitic serum but no antigen should show complete hemolysis.

If these results are obtained, the titration demonstrates that the antigenic mixture is capable of producing absolute inhibition of hemolysis in a dose as small as 0.05 c.c., and that it does not inhibit hemolysis in the presence of a normal serum even in four times that dose. Such an antigenic emulsion is suitable for use in the Wassermann test.

The amount of antigenic emulsion necessary to produce complete inhibition of hemolysis is known as an antigenic unit and in the test only one antigen unit is employed. *The unit is not doubled in making the test, as is the unit of complement and amboceptor.* A good antigen should show complete inhibition of hemolysis with a strong positive serum in a dose of 0.05 c.c. of a 1-10 emulsion, but an antigen giving the same result in a dose of 0.1 c.c. of a 1-10 emulsion is satisfactory in practical work.

Preparation of the Blood Suspension.—In the complement-fixation test for syphilis, as performed by the writer, each tube used in the test contains 1 c.c. of a 0.5 per cent suspension of human red blood corpuscles, prepared in the following manner:

The quantity of blood required for the tests will, of course, depend upon their number. One cubic centimeter of blood will furnish enough suspension for 200 tubes, or 100 tests, and unless one is doing a large number of tests, enough blood may be easily obtained by constricting the middle finger with a piece of rubber tubing and pricking the finger upon the dorsal side, just above the nail, with a sterile needle or glass point. The blood is collected into sterile graduated 10 c.c. centrifuge tubes, the tube being filled with sterile sodium citrate solution (20 grams sodium citrate to 1,000 c.c. of 0.85 or 0.9 per cent salt solution) up to 9 c.c. and allowing the blood to drop into the tube until it is filled up to the 10 c.c. graduation. The centrifuge tube is then well shaken and then centrifuged until all the corpuscles are collected at the bottom of the tube. The supernatant fluid is then poured off, the tube filled again with salt solution (not citrate solution) shaken thoroughly, and again centrifuged. This process is repeated four times when the corpuscles are washed sufficiently.

The supernatant fluid is poured off for the last time and the blood diluted

with enough salt solution to make a 5 per cent suspension. In the test 0.1 c.c. of this 5 per cent suspension is added to each tube which should contain 0.9 c.c. of salt solution, thus making approximately a .5 per cent suspension of the red blood corpuscles.

The blood corpuscle suspension must be kept in the ice box when not in use as it rapidly hemolyzes if kept in a warm room in summer time. It should preferably be prepared fresh for each day's work but if kept in a good ice box it may be used for two, and in some instances, for three days, provided titrations are made before the tests are proceeded with.

Collection of the Patient's Serum.—Many methods have been advocated for collecting blood for the Wassermann test and much special apparatus has been devised for this purpose. The simplest and best method is to remove from 2 to 5 c.c. of blood with a sterile glass syringe from one of the large veins in the arm ejecting it into a suitable glass bottle, allowing the serum to separate in the ice box, and pipetting the serum into a sterile glass tube vial for shipment or for storage prior to making the test.

The Wright capsule has been largely used in the army for the collection of blood for the Wassermann test and when properly used is a very simple and efficient method. The blood may be collected either from the lobe of the ear or the finger, filling the capsule about two-thirds full. The blood should be shaken into the straight end of the capsule after it has been sealed in the flame, being careful not to heat the blood during the sealing, after which the curved end of the capsule may be sealed.

Among the special apparatus that has been devised for this purpose, I have found the Keidel tube the most satisfactory. These tubes may be obtained from dealers in laboratory materials and furnish an excellent, although rather expensive method, of collecting blood for the Wassermann test.

Method of Performing the Wassermann Test.—I shall describe here the method of performing the Wassermann test which is generally adopted in the army and which was originally elaborated by me. The method has been used in the army since 1909 and has been given a very thorough trial, hundreds of thousands of tests having been made during this time, and I believe that it is the simplest and most accurate method of performing the Wassermann test that is in common use. Our experience with it in the army has been most satisfactory and its accuracy is proved by the fact that many thousands of our cases have been followed by this test and the results have agreed with the therapeutic results expected and, as many tests have been made upon the same individual, we have had an opportunity of discovering any variations in the results at different times which would certainly have occurred with an

imperfect method of performing the test. The method has been used by many different workers and the results have practically agreed.

Other methods of performing the test will be described briefly after this description, but personally I prefer this method because I have used it for ten years with satisfaction and know that it gives delicate and accurate results. Other methods are undoubtedly as accurate but this method has been found the most simple and the most adaptable to army practice and, if performed as described, will be found to be as well suited to civilian laboratories.

Technic of the Test.—Test tube racks containing two parallel rows of holes should be used and test tubes measuring approximately 10 cm. in length by 1.25 cm. in diameter are most convenient in practice.

Before making a series of tests the complement should be carefully titrated as already described. Some authorities prefer to titrate the amboceptor instead of the complement, but as the complement is the substance which is most apt to vary in strength it should be titrated in preference to the amboceptor. As a matter of fact, the titration of the complement with a fixed dose of amboceptor can not result in any fallacies in the test, as the amount of complement found necessary in the titration to produce hemolysis, when doubled, as it is in making the test, is always sufficient to give accurate results with the dose of amboceptor used.

For each serum tested two tubes are necessary, an *anterior* one, which is the testing tube, and a *posterior* or control tube. The anterior tubes contain the patient's serum with the syphilitic antigen, while the posterior contains the patient's serum without the antigen, thus acting as a control of the serum tested. Besides these two tubes there must be two control tubes containing a known syphilitic serum, and two containing a known normal serum, the anterior tubes in each case containing the syphilitic antigen as well. The sera used in the test must all be inactivated for ½ hour at 37° C.

In making the test proceed as follows: In each of the six tubes enumerated place 0.9 c.c. of normal salt solution. In tube I *anterior,* place 0.1 c.c. of the serum to be tested and the same amount in Tube 1, *posterior.* In Tube 2, both anterior and posterior, place 0.1 c.c. of the known syphilitic serum; in Tube 3, both anterior and posterior, place 0.1 c.c. of the known normal serum. Now add to each tube *two* units of the complement and to each *anterior* tube *one* unit of the syphilitic antigen, and incubate in a water-bath at 37° C. for one-half hour or in an incubator at the same temperature for one hour. At the expiration of this time add to each tube 0.1 c.c. of the 5 per cent suspension of human red blood corpuscles and *two* units of amboceptor paper. Incubate for one hour in the hot water-bath

at 37° C. or for two hours in an incubator at the same temperature, placed in the ice box for one hour, and then read the results. The tubes, after the amboceptor paper is added, should be shaken every fifteen minutes during the incubation, in order to liberate thoroughly the serum from the paper. Neglect of this will result in partial reactions in cases that should react negatively. The following table illustrates the method described:

TABLE VII

METHOD OF PERFORMING WASSERMANN TEST

SERUM FOR DIAGNOSIS	POSITIVE CONTROL SET	NEGATIVE CONTROL SET			
Anterior Tubes	Anterior Tubes	Anterior Tubes	Incubate for one-half hour in water-bath at 37° C. or for one hour in incubator at same temperature.	Add two units of amboceptor paper to each tube and 0.1 c.c. of .5 per cent suspension of human red blood corpuscles.	Incubate for one hour at 37° C. in water-bath or 2 hours in incubator.
Patient's serum, 0.1 c.c. Complement, 2 units Antigen, 1 unit Salt solution, 0.9 c.c.	Positive serum, 0.1 c.c. Complement, 2 units Antigen, 1 unit Salt solution, 0.9 c.c.	Normal serum, 0.1 c.c. Complement, 2 units Antigen, 1 unit Salt solution, 0.9 c.c.			
Posterior Tubes	Posterior Tube	Posterior Tube			
Patient's serum, 0.1 c.c. Complement, 2 units Salt solution, 0.9 c.c.	Positive serum, 0.1 c.c. Complement, 2 units Salt solution, 0.9 c.c.	Normal serum, 0.1 c.c. Complement, 2 units Salt solution, 0.9 c.c.			

If desired a *hemolytic* and *antigenic* control tube may be included but this is not necessary in practice if titrations have been made prior to making the test. If they are used they are prepared exactly as the other tubes except that no serum is placed in them, the same quantity of complement and antigen being used as in the test.

The results of the test should be as follows, if everything is working properly: The anterior tube containing the patient's serum, if it is positive, should show complete inhibition of hemolysis (positive reaction), while the posterior tube containing the patient's serum without the syphilitic antigen should show complete hemolysis. If the patient's serum is normal there should be complete hemolysis in the anterior tube (Tube 1) and various degrees of inhibition if the case is an early one or has received treatment. The posterior or control tube should always show complete hemolysis.

The anterior tube of Set 2, containing the known positive syphilitic serum should show complete inhibition of hemolysis (positive reaction), while the posterior tube of Set 2 should show complete hemolysis. If the posterior tube shows inhibition it demonstrates that the positive control serum is unsatisfactory.

The anterior tube of Set 3, containing a known normal serum, should show complete hemolysis, as should the posterior tube of this set.

If a hemolytic control tube is used it should show complete hemolysis and the antigen control tubes should also give complete hemolysis with the show complete hemolysis, as should the posterior tube of this set.

Nomenclature of Results.—The results of the Wassermann test are variously reported by different laboratories and it is essential that one be acquainted with the meaning of the terms employed in order to interpret the test as reported by these laboratories.

In the army we employ four designations in reporting the results of the test, double-plus (++) indicating complete inhibition of hemolysis, and therefore, a positive reaction; plus (+) indicating anything between complete inhibition and 50 per cent of inhibition of hemolysis; plus-minus (+–) indicating anything between 50 per cent of inhibition and complete hemolysis; and minus (–) indicating complete hemolysis, and therefore, a negative reaction. Plus and plus-minus reactions are always considered as doubtful reactions in the absence of a clear history of infection or of definite clinical symptoms of the disease.

In many laboratories the results of the test are recorded as four plus (++++) indicating complete inhibition of hemolysis, and three plus (+++), two-plus (++), and plus (+), indicating lesser degrees of inhibition of hemolysis. Comparing these designations with the ones used in reporting the test in the army, the three- and two-plus reactions would correspond with our plus reaction, the four-plus with our double plus, and the one-plus with our plus-minus reactions.

The physician should become thoroughly familiar with the nomenclature used by the laboratory to which he sends his tests and the significance to be attached to each grade of the reaction reported from that laboratory. Otherwise, serious errors would develop in the interpretation of the reaction, especially if tests were made at two different laboratories in which the nomenclature differed.

Other Methods of Performing the Wassermann Test.—A brief description will here be given of the original method of performing the Wassermann test, as used by Wassermann,

Neisser and Bruck, and the most used of the many modifications of the test.

The Original Wassermann Technic.—The original Wassermann test was made with a sheep hemolytic system and an aqueous extract of fetal syphilitic liver as antigen. The complement was fresh guinea pig serum and the sera to be tested were inactivated at 56° C for one-half hour. All reagents were carefully titrated before use. Three tubes were used for each serum tested, three for the known positive, three for the known negative, and three tubes for control of the hemolytic system. The test was performed as follows as described by Thompson:[13]

Into the first tube of each serum tested, including the positive and negative sera, is placed 1 c.c. of a 1 to 5 dilution of antigen and into the second, 0.5 c.c.; the third tube receives no antigen. The first and third tubes receive 0.2 c.c. of inactivated serum and the second 0.1 c.c. Each tube, including the first two of the hemolytic system control, receives 1 c.c. of the diluted guinea pig serum (1-10), and the total amount is made up to 3 c.c. The tubes are now incubated for one hour at 37° C., after which 2 units of amboceptor, diluted so that each cubic centimeter contains 2 units, and 1 c.c. of the corpuscle suspension (5 per cent suspension) are added to each tube, except the last two tubes of the hemolytic system control, to each of which are added 1 c.c. of salt solution and 1 c.c. of corpuscle suspension. The incubation is now continued for two hours when the tubes are placed in the ice box overnight. The following morning the results are read as follows: If tubes 1 and 2 of a serum show complete inhibition of hemolysis, the corpuscles having settled to the bottom, and the fluid above being perfectly clear and free of color, the reaction is strongly positive and designated ++++. If Tube 1 shows complete inhibition and Tube 2 faint hemolysis, the reaction is designated +++ or positive. If Tube 1 shows complete inhibition of hemolysis and Tube 2 complete hemolysis, the reaction is recorded as ++; while if Tube 1 shows partial hemolysis and Tube 2 shows complete hemolysis, the reaction is faintly positive and marked +. If Tube 1 shows doubtful binding of complement and Tube 2 shows complete hemolysis, the reaction is doubtful and designated +−. Complete hemolysis in both Tubes 1 and 2 constitutes a negative reaction and is recorded −.

Both Tubes 1 and 2 of the negative control should show complete hemolysis and 1 and 2 of the positive control complete inhibition or hemolysis. Tube 3 of all sera should show complete hemolysis as no antigen is placed in these tubes. Tube 1 of the hemolytic system control tubes should show hemolysis and Tubes 2 and 3 complete inhibition.

Noguchi's Modification.—In this modification the human hemolytic system is used, the antigen is the acetone-insoluble

extract of normal organs already described, and the serum of the patient is tested without being inactivated. The test is performed as follows, as described by Noguchi.[14]

Put into each of two small test tubes front and rear one drop (0.02 c.c.) of the serum to be tested from a capillary pipette. (When using inactivated serum put 4 drops 0.08 c.c. into each tube. Use 0.2 c.c. of cerebrospinal fluid not inactivated). Add to each tube 0.1 c.c. of 40 per cent fresh guinea pig serum made by adding one part complement to 1½ parts of 0.9 per cent salt solution. To the front tube add the antigen. Then to both tubes add 1 c.c. of the 1 per cent suspension of washed human corpuscles. Allow the tubes to incubate in a water-bath at 37° C. for one half hour. (A positive and normal control should be prepared in the same way as the patient's serum, making a set of six tubes in all.) After incubation add to each tube a slip of the impregnated amboceptor paper containing two units of the amboceptor and incubate in the water-bath for one hour at 37° C. After final incubation the tubes should be kept at room temperature for a few hours before the results are recorded.

This modification of the Wassermann test is an excellent one and has proved very useful in practice. Its advantages consist in the small amount of the reagents needed in making the test and the simplicity of the technic. For army purposes, however, it is not as practicable a method as the one recommended in this contribution.

Tschernogubow's Modification.[15]—This investigator uses a modification of the test in which both complement and amboceptor are obtained from the patient's blood to be tested. This method makes it imperative that the blood be tested in the active condition; the antigen used is an alcoholic extract of normal liver, while the corpuscles are those of the guinea pig. This method will not be described as, in other hands than those of the originators, the method has not proved very satisfactory.

Bauer's Modification.[16]—This modification consists in the use of the natural amboceptor against sheep's corpuscles present in human blood serum, as amboceptor. In all other respects his method is similar to the original Wassermann.

Hecht-Weinberg's Modification.[17]—In this method the amboceptor is that present in the serum to be tested, while the complement is also that naturally present in the tested serum. It

is thus necessary that the serum be used without inactivation in this method. The cells used are sheep corpuscles and the antigen an alcoholic extract of human heart. This method, especially as modified by Gradwohl,[18] has given good results in routine work, but it is not recommended in preference to either the original Wassermann or the author's method.

Other Modifications.—Several other modifications of the Wassermann test have been advocated from time to time. Noguchi's, which is probably the best, has already been noted. In addition we have Browning and McKenzie's[19] in which the corpuscles of the ox are used for the blood suspension and an alcoholic extract of human heart as antigen; Boas,[20] who uses goat corpuscles and the alcoholic extract of human heart; and that of Brezovsky,[21] whose method is like the original Wassermann method with the exception that horse corpuscles are used instead of sheep corpuscles and the amboceptor is prepared by immunizing rabbits to these corpuscles.

It may be stated that in the hands of the various originators of the methods mentioned, all have given excellent results, but most of them require very careful attention to technical details and when used by the tyro are very apt to lead to erroneous results. The method of performing this test recommended by the author is simple, easily learned, and possesses the advantage that it has been given a thorough trial for years by several observers in the military service, and the results have been checked by thousands of repeated examinations upon treated patients.

The Interpretation of the Results of the Wassermann Test.—Owing to the many misconceptions prevalent in the profession regarding the exact value to be placed upon the various degrees of reaction as reported from different laboratories and the exact meaning of a positive or negative Wassermann reaction in suspected cases, the subject of the interpretation of the results of the test is of primary importance. In my experience more than a score of cases have been diagnosed as syphilis upon the report of a plus-minus or plus Wassermann reaction and hundreds of patients have been assured by their physicians that they were free from the infection upon the strength of a single negative reaction. Such interpretations of the results of this test are absolutely unjustifiable and have caused much misery and

have led to a feeling of doubt as to the real value of this test among quite a number of physicians who would otherwise make wide use of it in their practice.

In order to correctly interpret the results of the test it is necessary that the physician be thoroughly familiar with the nomenclature used in reporting the results of the test in the laboratory that he patronizes and the relative value to be attached to each type of result. I have already mentioned the nomenclature used in the army and that employed by most laboratories, and it is the belief of most authorities that a diagnosis of syphilis based upon the Wassermann test *alone* should not be made unless there is absolute inhibition of hemolysis, i. e., a double-plus reaction, as reported by the army laboratories, or a four-plus, as reported by many other laboratories. If symptoms are present lesser degrees of the reaction may be considered as diagnostic, and this is especially true in early primary cases, where a single plus reaction is often encountered.

As a result of our studies of syphilis in the army the following conclusions appear to be justified regarding the interpretation of the results of the Wassermann test:

1. If the diseases, other than syphilis, that sometimes give a positive result with the Wassermann test, can be excluded, a double-plus (four-plus) reaction is diagnostic of the disease. Under such conditions I consider this type of reaction as absolutely specific, whether symptoms are present or not, or whether there is or is not a history of infection.

2. Under the same conditions, a plus reaction (three-plus or two-plus of some writers) may, in primary, tertiary, or latent infections, be regarded as diagnostic, provided there is a clear history of infection or clinical symptoms are present. In the absence of either, a plus reaction should not be regarded as diagnostic of the disease.

3. A diagnosis of syphilis should never be based upon a plus-minus reaction. Many perfectly normal individuals give this type of reaction and it is of no value in the diagnosis of the disease except that it should be considered as negative.

4. A single negative reaction, where there is no history of infection and where symptoms are not present, is of considerable value as a corroborative sign of the absence of syphilis, but

where there is any suspicion that the disease may be present it has no eliminating value. As will be noted later, many factors may render a Wassermann reaction negative at times when it should be positive, and it is only when a negative reaction persists over a long period of time that it can be considered as good evidence of the absence of the disease and even in these cases, the spinal fluid should be tested before the patient can be assured that he is free from the disease. The above remarks are also true of treated cases, a single negative reaction being of practically no value as indicating a cure. In such cases a provocative reaction should be made, which, if negative, should be followed by a Wassermann upon the spinal fluid. If this is negative it would be well, in many cases, to have a luetin test made before the patient is considered as cured.

As I have stated elsewhere, the interpretation of the results of the Wassermann test must rest very largely with the clinical picture present and it is the clinician's place to reconcile the result of the test with the clinical picture rather than the serologist's. The latter simply reports what actually occurs when the patient's blood serum is tested and it remains with the clinician to interpret this report in the light of the patient's history and symptoms.

Factors Influencing the Result of the Wassermann Test. The Ingestion of Alcohol.—The ingestion of relatively large amounts of alcoholic liquors will markedly influence the results of the Wassermann test, in the way of making a positive result negative. This fact was first noted by Major Nichols and myself[22] and the results of our investigation of the subject were published in 1911, and have since been confirmed by many observers. In brief, we found that the ingestion of alcohol in the form of beer or whiskey, as well as alone, and in amounts varying from 180 to 240 c.c. of whiskey and 700 c.c. of beer, often caused a positive Wassermann reaction to become negative and that the blood serum might remain negative for as long as three days, although generally it became positive again within twenty-four hours. Smaller amounts of alcoholics will also render strong plus reactions negative and thus give an erroneous impression regarding the results of treatment.

This fact renders it very important that blood for the Was-

sermann test should not be collected until after careful inquiry has been made regarding the use of alcohol within the last twenty-four hours before collection, and if alcohol in any amount has been ingested the collection of the blood should be deferred for at least one day. Even small amounts of alcoholic liquors may render a plus reaction negative, and thus where the test is being used as a control of treatment, obscure the real condition of the patient as regards his serologic status.

Variations in Amount of Complement Inhibiting Substance.—In 1914, I published certain observations[23] showing that in every stage of syphilis variations occur in the blood serum from day to day sufficient to cause a double-plus (four-plus of some writers) or positive, reaction to appear and disappear within so short a period of time as one week. These experiments were made upon prisoners at the U. S. Military Prison at Fort Leavenworth, who were under most strict discipline and upon a routine diet, so that the question of alcohol as influencing the results of the test could be absolutely excluded. The tests were made every day for a week in each case upon samples of blood collected upon the same day, and it was determined by titrations of these samples that great variations occurred in the strength of the Wassermann reaction from day to day and that these variations must be considered in using the test in the diagnosis, or as a control of the treatment, of syphilis. That these variations were due to variation in the hemolytic system, as thought by some writers, is disproved by the fact that before each series of tests careful titrations were made of the reagents used, so that such variations were impossible. My results have since been confirmed by those of others and there is now no doubt that the substance or substances giving rise to the Wassermann reaction do vary markedly in some instances and that a positive reaction of today may become negative within as short a period as twenty-four hours, so that upon the morrow, if the blood be tested by another laboratory, a negative result will be returned.

Briefly summarized, my results showed that in one primary case of syphilis a plus or doubtful reaction was obtained on three of the seven days during which the serum was tested, the reaction upon four days being double-plus or positive; in another case a plus or doubtful reaction was obtained upon two of the

seven days. In one case of secondary syphilis a negative reaction was obtained upon one day, a plus-minus on one day, a plus on three days, and a double-plus or positive on two days; in another secondary case a plus or doubtful reaction was obtained on two of seven days. There were, however, several primary and secondary cases that gave a double plus or positive on all of the seven days of the test. Similar results were obtained in latent infections, and they all go to prove how valueless a single negative Wassermann reaction is in the elimination of syphilis in a suspected individual.

Growth of Bacteria in the Blood Serum.—I have shown that the growth of certain bacteria in specimens of blood serum may produce a false positive reaction with the Wassermann test. These observations, published in 1911,[24] proved that such common organisms as streptococci and staphylococci, when developing in blood serum, may give rise to substances which will cause a positive Wassermann reaction. A temperature of about 37° C. is required for the development of these substances but this temperature may often be reached in specimens of blood serum in the summer, even in temperate climates, and very often in tropical ones. It was found that Staphylococcus albus and Staphylococcus aureus when growing at this temperature in blood serum sometimes produced a positive reaction, the serum being previously negative, and the same was true of a short chain streptococcus isolated from a blood serum. That every strain of a certain bacterial species will not do this was shown by the fact that while a double-plus reaction occurred in a blood serum infected with a stock staphylococcus and with an S. aureus isolated from a serum, a negative result was obtained with another S. aureus isolated from an infected serum which gave a negative reaction.

The fact that under certain conditions such common organisms as staphylococci and streptococci may give rise to false reactions when growing in blood serum may lead to the conclusion that only absolutely fresh sera should be tested, but if proper precautions are used in collecting the blood for the Wassermann test, there will be no trouble from bacterial infections of the serum, for our experiments have shown that if the blood serum is sterile it may be kept at room temperature,

even in summer weather, for as long as a month without danger of a negative serum becoming positive, although sera kept in this way are very apt to develop inhibitory substances which inhibit hemolysis in both the tube containing antigen and the control tube. Infected sera may be easily detected by their cloudy appearance and disagreeable odor, and such sera should be discarded.

Whenever blood serum is to be kept for more than 24 hours before being tested great care should be taken that the blood is collected aseptically. The needle or lancet used for puncture and the tube or other container in which the blood is collected should be sterilized and the skin over the site of puncture thoroughly washed with alcohol and allowed to dry and then painted with iodine.

Besides the factors mentioned there are certain features connected with the technic of the Wassermann test that are of immense importance if one is to avoid erroneous results. Thus the quantity of serum tested with the particular method of making the test that may be selected must be strictly adhered to, for normal blood serum will give a positive reaction if enough of it is used in the test and any positive serum may give a negative reaction if too little is used. For each method of making the test the maximum amount of blood serum must be ascertained and this amount should never be exceeded even if certain normal sera react negatively with a larger amount.

Another factor in the technic of the utmost importance is the daily titration of the complement before each series of tests. Guinea pig serum varies very greatly as regards its complementary strength, and anyone who undertakes to use the same amount of guinea pig serum for every series of tests will make grievous errors and many innocent individuals will be diagnosed as syphilitic. Although this is true, in many Wassermann laboratories the complement is not titrated, a given dose being used in every series of tests, an omission of fundamental importance if accurate results are desired. The Wassermann reaction is absolutely quantitative in nature and unless all the reagents used are accurately titrated erroneous results are sure to occur.

The Specificity of the Wassermann Reaction.—As I have already stated the Wassermann reaction can not be considered as absolutely specific for syphilis, for positive results do occur with other disease processes. While this is true, it is also true that a positive reaction with this test indicates syphilis in so immense a proportion of individuals giving it that the practical value of the test is hardly at all influenced by the very few instances in which a positive result is obtained in other conditions.

In my own experience, I have obtained twelve positive reactions among 4,000 individuals suffering from diseases other than syphilis, or 0.3 of 1 per cent. Of these, five were suffering from tertian malarial fever, the blood being positive during the febrile attacks but negative in the intervals; three were diagnosed as tuberculosis; three as pityriasis rosea; and in one the diagnosis was undetermined. In the cases diagnosed as tuberculosis there was every reason to believe that syphilis might also have been present, while in fact two gave a clear history of syphilitic infection; while in the cases of pityriasis rosea the reactions, while almost double-plus, would not have been returned as positive without a qualifying statement. However, even if all of these cases were really false reactions, the number is so small as to be of no practical importance as an argument against the specificity of the test from the clinician's point of view. Vedder[57] has had similar results with the test, having only four false positives in 1,049 individuals suffering from diseases other than syphilis, or 0.4 of 1 per cent. While it can not be claimed that the Wassermann test, when positive, is absolutely diagnostic of syphilis, from a practical standpoint it is doubtful whether a more specific test is used in medicine, the margin of error appearing to be less than 0.5 of 1 per cent.

When the Wassermann test was in its infancy, positive reactions were reported in a great number of different diseases, but as we have gained experience in its application and technic the number of conditions in which a positive reaction may be expected has become smaller and smaller, until today, a serologist who reports positive reactions in any number in nonsyphilitic conditions is not deserving of the confidence of the profession, for such reports are absolute proof of the inaccuracy

of his technic. Of the few conditions in which a positive Wassermann reaction sometimes occurs may be mentioned leprosy; relapsing fever; yaws, a disease very closely related to syphilis, and due to a spirochete; malarial fevers, during the febrile stage; and diabetes, when acidosis is present. The reaction has been reported as positive in scarlet fever, pellagra, and certain septic conditions, but my experience has been that the test does not give a positive reaction in such conditions and that the reactions reported have been due to faulty technic or an erroneous reading of the results of the test.

The Percentage of Positive Results in the Various Stages of Syphilis.—The following table gives the percentage of positive results I have obtained with this test in 5,600 cases of syphilis observed in the army, the tests having been made personally. This table agrees with those published by most observers and gives an accurate index of what may be expected from the test in the various stages of the disease.

TABLE VIII

PERCENTAGE OF POSITIVE RESULTS IN 5,600 CASES OF SYPHILIS

STAGE	TOTAL CASES	POSITIVE	PER CENT	NEGATIVE	PER CENT
Primary	1081	971	89.8	110	10.1
Secondary	2217	2132	96.1	85	4.9
Tertiary	728	633	87.4	95	13.5
Latent	1525	1039	68.1	486	31.8
Congenital	28	25	89.2	3	10.7
Parasyphilis	22	15	68.1	7	31.8
	5600	4815	85.9	786	14.0

In the vast majority of the cases tested in this table only one Wassermann test was made and it is undoubtedly true that had several tests been made in these cases a much larger percentage of positive results would have been secured. However, under ordinary conditions, it is evident that in primary syphilis we may expect about 90 per cent of positive results and that at least 10 per cent will prove negative; that about five per cent of secondary cases will prove negative; about 13 per cent in the tertiary stage; and about 30 per cent in the latent stage. The figures given for congenital and parasyphilitic cases are too few in number to be reliable but the consensus of

opinion of numerous investigators is that we may expect about 95 per cent of positive reactions in congenital syphilis; about 98 per cent of positives in paresis; about 70 per cent in tabes; and from 50 to 60 per cent in cerebrospinal syphilis.

The Date of the Appearance of the Reaction in Syphilitic Infection.—There appears to be a considerable amount of confusion regarding the time that the Wassermann reaction may be expected to be positive in syphilitic infections, and as this is an important practical question, it deserves careful consideration. It is now well known that the earlier in a syphilitic infection the proper treatment is begun, the better are the chances for cure, so that unless the Wassermann test gives a reasonable number of positive reactions in early primary cases, it is not of much value in the diagnosis of the disease just when a diagnosis is of the most vital importance to the patient. While the ideal method of diagnosing these early infections is by the use of the dark-field apparatus and the finding of the spirochete in the fluid from the initial lesion, it is often impossible to avail oneself of this method and the physician naturally turns to the Wassermann test for diagnostic help. Some authorities have unfortunately given the impression in their writings that this test is of very little value in diagnosing syphilitic infection in the primary stage of the disease, but my personal experience in this direction has been the opposite, and I believe that the Wassermann test is a most valuable aid to the physician in the diagnosis of primary stage of syphilis. Nearly 90 per cent of primary cases that I have tested have shown a positive reaction, if repeatedly tested, before the appearance of secondary symptoms, and while a single test, performed very early in the primary stage, will be found negative in a large majority of the cases, repeated tests will prove that the reaction becomes positive some time before the appearance of secondary symptoms in the vast majority of cases.

Table IX is compiled from personal observations and gives the date of the appearance of the positive reaction in periods of weeks after the appearance of the initial lesion, and is based upon 600 cases of primary syphilis in which the data regarding the age of the infection could be accurately ascertained.

TABLE IX

DATE OF APPEARANCE OF WASSERMANN REACTION IN WEEKS AFTER APPEARANCE OF INITIAL LESION IN 600 CASES OF PRIMARY SYPHILIS

WEEK AFTER APPEARANCE OF CHANCRE	TOTAL CASES	POSITIVE	PER CENT	NEGATIVE	PER CENT
First week	77	27	36.3	50	64.9
Second week	155	92	59.3	63	40.3
Third week	158	109	68.9	49	31.0
Fourth week	167	129	77.2	38	22.7
Fifth week	43	35	81.3	8	18.6

An analysis of this table is of interest. It will be noted, that in my experience, 36 per cent of primary cases of syphilis have given a positive reaction with this test up to the end of the first week from the time the chancre was first noted; almost 60 per cent during the second week; almost 70 per cent during the third week after the appearance of the initial lesion; over 77 per cent during the fourth week; and over 80 per cent five weeks after the appearance of the lesion. These figures prove conclusively that the Wassermann test is most useful in the diagnosis of syphilis during the primary stage of the disease and that its use should never be neglected in a suspected case or where a dark-field examination can not be obtained.

If there is one thing that the modern researches upon syphilis have clearly proved it is that the morphology of a sore is of little value in the diagnosis of syphilis, for the Wassermann test has shown that many so-called "soft-sores" were really chancres and that the typical Hunterian chancre is almost as much the exception as the rule. The best authorities admit that they have often failed to recognize the primary lesion of syphilis in atypical and innocent looking sores upon the penis, and, for this reason, every patient showing a sore in this region should be examined by the dark-field or have a Wassermann test performed as soon as possible, and, if negative, repeated at intervals until all danger of a positive reaction ceases to exist. We now know that treatment applied before the appearance of secondary symptoms is much more apt to prove successful in curing the infection than after such symptoms appear, and the physician who waits for the appearance of secondary symptoms before beginning treatment, when it is possible for him to have

a dark-field examination made or the Wassermann test applied, is criminally negligent, in my opinion, for with these aids it is possible to diagnose correctly practically every syphilitic infection before the appearance of secondary symptoms.

The Wassermann Test as a Control of the Efficacy of Treatment.—In the army we have found that the Wassermann test is invaluable as a control of the efficacy of the various methods of treatment that have been adopted from time to time. As an illustration of the extent to which the test has been used for this purpose in the military service I may state that I have made over twenty thousand tests upon treated cases, all for the purpose of controlling the treatment, and my experience has been that of all other medical officers who have had charge of army laboratories where Wassermann tests are made.

By means of the Wassermann test, repeated at intervals of a month or two months, it is possible to secure a clear idea of the efficiency of the method of treatment employed in any particular case and, in the vast majority of instances, to diagnose a clinical relapse long before other symptoms are present. The advantage of an early diagnosis of relapse is obvious, for, in most syphilitic infections which have apparently been cured, the first symptom of a relapse is the return of a positive Wassermann reaction, and this may occur weeks or even months before marked clinical symptoms are noted. For this reason all cases of syphilis that have been treated should be tested at frequent intervals in order to ascertain the effect of the treatment upon the reaction, and after the reaction becomes negative, a test should be made at least every three months for a period of at least one year, when, if the test still remains negative, a Wassermann should be made upon the spinal fluid and a luetin test before any patient is pronounced cured.

The use of the test as a control of treatment has resulted in increased knowledge regarding the value of both mercury and arsphenamine in the treatment of the disease and has added much to our knowledge of the action of other drugs that have been vaunted as specifics for syphilitic infection. In addition, it has shown that the absence of symptoms for long periods of time is no criterion of the cure of the disease, and that the physician who assures his patient that he is cured because of

the absence of symptoms does him a great injustice, unless the Wassermann test has been negative for at least a year and the other tests mentioned are also negative.

The Provocative Wassermann Test.—The provocative Wassermann test was first advocated by Gennerich[26] as a test for the cure of syphilis. He found that patients who had given a negative Wassermann reaction for long periods of time, if given a small dose of arsphenamine, would sometimes give a positive reaction afterwards, this type of reaction generally occurring within 48 hours but sometimes not until six or seven days after the injection. Recently several authors have endeavored to prove that this provocative test is of no value and that the positive reaction observed after it has nothing to do with the injection of arsphenamine but is explained by the normal variations in the strength of the reaction, as shown by myself and others. However, my personal experience with the test is sufficient to convince me that it is most valuable, not only in ascertaining whether syphilitic infection is cured, but also in the diagnosis of the disease in the primary or early secondary stage when the ordinary Wassermann test is negative. In applying the test from 0.3 to 0.4 gm. of arsphenamine should be given intravenously and the blood tested every twenty-four hours for a week afterward.

Table X is illustrative of the results obtained with the provocative test in cases that have given a negative result with the ordinary Wassermann test for several months.

TABLE X

RESULTS OF THE PROVOCATIVE WASSERMANN TEST IN SYPHILIS

CASE NO.	TIME SINCE TREATMENT	RESULT OF WASSERMANN TEST	RESULT OF PROVOCATIVE TEST
1	Months–15	Negative	Positive
2	Months–16	Negative	Negative
3	Months–17	Negative	Positive
4	Months–18	Negative	Positive
5	Months–19	Negative	Positive
6	Months–21	Negative	Negative
7	Months–24	Negative	Negative
8	Months–24	Negative	Negative

An inspection of this table will show that cases of syphilis which have been negative with the ordinary Wassermann test

for periods of 15, 17, 18, and 19 months gave a positive reaction after the administration of arsphenamine in the way mentioned, thus proving that the infection was not cured. In this way the provocative test has proved of great service in the army and it is my belief that no case of syphilitic infection should be considered as cured until this test has been applied.

As stated, the provocative test is also valuable in diagnosis, as I have several times observed early primary cases in which the test proved positive although the ordinary Wassermann was negative. It is my belief that in these early primary cases the provocative test should be used much more extensively than it has been, and that its use would result in a considerable increase in the number of positive reactions at this stage of the disease, and consequently in better therapeutic results as the disease would be recognized earlier than it is at present. The provocative reaction should also prove of value in other stages of syphilis in which the symptoms are suspicious but the ordinary Wassermann test is negative.

The Wassermann Test upon the Cerebrospinal Fluid.—It has only been recently that we have recognized that in every instance of suspected syphilis a Wassermann test should be made upon the cerebrospinal fluid as well as upon the blood, if we are to expect the most accurate results in diagnosis and treatment. Practically, this procedure is comparatively seldom made use of, and the consequence is that most of our cases do not have the cerebrospinal fluid tested although there is no question that it should be tested in every suspicious case where the blood Wassermann is negative and, if possible, even where the blood test is positive. Only by so doing can we be sure that the central nervous system is free from involvement and can assure our patient that danger from such involvement does not exist in cases where the blood Wassermann has been negative for long periods of time.

The method of making the test upon the cerebrospinal fluid is exactly like that for making the test upon the blood, except that larger quantities of the fluid are used than of the blood, and the fluid is not inactivated. With the method advocated in this contribution, I recommend the testing of 0.1 c.c., 0.2 c.c., 0.5 c.c. and 1 c.c. of the serum not inactivated. If a double-plus

reaction is given with quantities as small as 0.1 c.c., 0.2 c.c. and 0.5 c.c., it is probable that the diagnosis is paresis while if such a result is only found with 1 c.c. of the fluid the diagnosis is probably cerebrospinal syphilis or tabes.

It was formerly believed that in cases of cerebrospinal syphilis the blood gave a positive Wassermann while the cerebrospinal fluid was negative, in cases presenting nervous symptoms, but it is now known that if enough of the cerebrospinal fluid is tested, the reaction will be found positive in practically all cases of cerebrospinal syphilis. In paresis, in the vast majority of cases, the Wassermann is positive in both the blood and spinal fluid, while in cerebrospinal syphilis the Wassermann is often negative in the blood but positive in the spinal fluid if amounts as large as 1 c.c. are used, and it is important to remember these facts in differentiating the two conditions with the aid of the Wassermann test.

As regards the percentage of positive reactions that may be expected with the Wassermann test when applied to the cerebrospinal fluid in conditions of the nervous system, the following may be stated:

In paresis the test is positive in the blood and cerebrospinal fluid in practically 100 per cent of the cases, if 1 c.c. of the fluid be used in the test, while if smaller quantities are used, the percentage decreases, until, when but 0.2 c.c. is used, only about 75 per cent of paretics will show a positive cerebrospinal fluid. The same statement is true of patients suffering from cerebrospinal syphilis, nearly 100 per cent giving a positive reaction with 1 c.c. of the cerebrospinal fluid, but when only 0.2 c.c. of the fluid is used, only about 10 per cent gave a positive reaction. From these results it is apparent that in endeavoring to differentiate these two conditions by means of the Wassermann test upon the cerebrospinal fluid, it is necessary to titrate the latter, and that a positive result with 0.2 c.c. of the fluid or less is diagnostic of paresis, in the vast majority of cases.

In tabes the cerebrospinal fluid gives a positive reaction with the Wassermann test in over 90 per cent of the cases, if 1 c.c. of the fluid is used in making the test, but if only 0.2 c.c. is used the

percentage of positive results will only be from 5 to 10 per cent. In the blood, in tabes, the Wassermann is positive in about 70 per cent of the cases.

It is evident from what has been stated that the results of the Wassermann test in the cerebrospinal fluid depend entirely upon the amount of the fluid tested and this amount will vary with the different methods of making the test. In differentiating between paresis, tabes, and cerebrospinal syphilis, smaller amounts than 1 c.c. should be used, if the method recommended here is adopted, and an accurate titration of the fluid be made, as only in this way can the test be of any value in differentiating between these conditions. In addition the cell count and the amount of globulin present should be ascertained, as has been stated elsewhere in this volume.

From this rather brief consideration of the Wassermann test and its uses in the practice of medicine I believe that it must be evident to all conscientious practitioners that the test is a most valuable one in the diagnosis and control of the treatment of syphilis and that it is a test that one would be almost criminal to neglect in the practice of medicine among those afflicted with this protean disease. The test has been thoroughly investigated for a period of nearly ten years and, despite the fact that careless technic in the hands of inexperienced laboratory assistants has injured it in some localities, it stands today as the most generally useful method that we possess in the diagnosis of syphilis and as a control of the treatment of the disease. It has made possible the diagnosis of the disease in individuals in whom no visible signs of syphilis have been present for many years and has rendered the differentiation of syphilis from other diseases of the central nervous system certain and practical. So important a place has this test earned in the practice of medicine that it may be truthfully stated that the diagnosis of syphilitic infections and the proper control of their treatment is, at the present time, based upon the results of serologic examinations, and that the failure to use the Wassermann test in either diagnosis or as a control of treatment is inexcusable and the physician who does so is doing a grave injustice to his patients.

Other Serologic Tests

In addition to the Wassermann reaction and its various modifications, other serologic tests have been devised which do not depend upon the principle of complement fixation. However, none of them have stood the test of time the way the Wassermann has, and we think but little of any of them.

Cobra Venom Test.—This test was devised by Weil[27] in 1909 and depends upon the observation that the hemolyzing effect of cobra venom upon human red blood corpuscles in the natural individual is much more marked than in the syphilitic. It is not as sensitive or as reliable as the Wassermann.

Precipitin Tests.—Olitsky and Olmstead[28] have investigated the various precipitation tests, especially that devised by Herman and Perutz[29] and have concluded that for practical purposes they possess no value.

Enzyme Test (Abderhalden).—Varney and Morse[30] have carefully investigated the diagnostic importance of this test in syphilis and have reported favorably, although they apparently found it not so sensitive as the Wassermann. Their article may be consulted for details.

Landau's Color Test.[31]—This test is no longer used, for various workers have learned that it was not reliable.

Butyric Acid Test.—This test was discovered by Noguchi who noted that the blood serum of syphilitics contained more globulin than did normal serum. It is but little used on blood serum.

The Gel Test.—The "Gel" test was originally described by McDonough, but Strickler's[31a] investigations have not proved it satisfactory, and undoubtedly it will soon be heard of no more.

The account by Craig gives admirably the value of the Wassermann reaction from the standpoint of the laboratory man, and also the view adopted by many experienced syphilologists, particularly those with a large experience in the clinics. However, a word or two more might be said from the standpoint of private practice.

Within the past year the author of the book has seen no fewer than six cases which had been diagnosed as syphilis on the strength of positive reactions performed in various small towns. In every instance our results in Washington were absolutely negative, and clinically there was no real reason to suspect the dis-

ease in any case. It is obvious, then, that much harm can be done by inexperienced workers.

Also it is necessary to say a word or two in connection with the commercial laboratories, which give a ready-made diagnosis in return for some blood and a fee. I feel absolutely that the diagnosis must be made from both the laboratory and the clinical findings and that any commercial way of establishing a diagnosis is apt not to be for the best interests of the community. It can not be too strongly emphasized that all Wassermann reports must be interpreted with care and caution and that frequently this can only be done by an experienced syphilologist.

The Luetin Reaction

Noguchi[32] first perfected an allergic reaction that was of value in syphilis and that compared with the cutaneous tuberculin tests. He states that he was stimulated to this work by Dr. Wm. H. Welch. Luetin consists of pure cultures of Treponema pallidum and is derived from six different strains. It is made in a way similar to ordinary bacterins. Its sterility is tested both culturally and biologically.

In testing an individual an all-glass very fine syringe, graduated in one-hundredths of a cubic centimeter is employed. For an adult 0.035 c.c. of luetin is drawn into the barrel and then an equal amount of sterile normal saline solution, and the two are mixed and then injected into the skin, not into the subcutaneous tissue. A slight raised wheal must be produced or the injection is too deep. This will disappear in less than an hour. In children about three-fifths of the adult dose is employed.

Reactions are of the following type, negative, papular, pustular, hemorrhagic and delayed.

In case of a negative reaction the following phenomena are usually displayed; at the end of a few hours there is a slight red macule, or in some instances a maculopapule that disappears in less than three days; this is due to irritation and trauma and is not specific. In other instances there may be absolutely no reaction whatever.

The papular reaction usually does not appear for forty-eight hours and is at its height in from four to five days after injection. In diameter it is usually about two-thirds of a centimeter

and it may be surrounded by an inflammatory areola. To the palpating finger a distinct induration can be felt. This reaction disappears in from four to ten days.

The pustular reaction is simply a more severe type, and commences just as does an ordinary papule. Then vesicles form and finally a pustule: this is accompanied by some pain and itching. The lesion resolves just as does an ordinary pustule. This type of reaction is stated to be most frequent in congenital or acquired syphilis of long standing.

A hemorrhagic form rarely occurs: this runs about the same course as the pustular one.

In the delayed reaction at first there are no changes but in about four weeks a typical reaction develops.

Since 1911 the luetin has been tested by many men. Noguchi's late paper[33] gives the following figures: In primary syphilis it is positive in less than 30 per cent of the cases; in secondary syphilis it is positive in 47 per cent; in tertiary cases it is positive in 80 per cent; in congenital syphilis it is positive in about 70 per cent; in syphilis of the central nervous system it is rarely positive in acute meningitis but is positive in tabes and paresis in about 60 per cent of the cases; in visceral syphilis it is frequently positive, in aortic insufficiency it is stated to be positive in nearly 90 per cent of the cases, and my own experience agrees with these findings.

The following authors, among others, have reported upon the results from luetin: Robinson,[34] Howard Fox,[35] Simpson,[36] Schmitter,[37] Rytina,[38] Pusey and Stillians,[39] Gay[40] and Hanes.[41]

The majority of observers have noted that the luetin reaction is much more strongly marked in those who have received treatment, but it remained for Sherrick[42] to show that individuals who were definitely nonsyphilitic, would show a positive luetin reaction in a very high percentage of cases if they had previously taken potassium iodide or other iodine containing drugs. This observation has been confirmed by both Lyons,[43] Cole,[44] and Kolmer, Matsunami and Broadwell.[45] Stokes[46] has shown that in syphilis and in certain other diseases the injection of agar will produce a typical luetin reaction. Cole reports that the reaction will remain positive for at least three weeks after the iodine has been discontinued.

From these observations it can readily be seen that the use of luetin is worse than useless in persons who have recently taken any of the iodides, for it may lead to an erroneous diagnosis. And at times it is very difficult to tell whether or not iodides have been taken. Also it is possible that other substances may sensitize the body as to favor the production of a reaction. Consequently its use as a diagnostic agent must be accepted with great reserve. However, a negative luetin reaction may be of considerable value in excluding late syphilis.

THE ROENTGEN RAY DIAGNOSIS OF SYPHILITIC LESIONS

By Walter Van Sweringen, Capt. M.R.C., U.S.A., and H. H. Hazen, M.D.

Unquestionably the roentgen rays are of more value in determining the presence or absence of syphilis in certain organs than they are in making a general diagnosis of syphilis. However, x-ray examination will frequently reveal a syphilitic lesion that has been previously overlooked by the clinician. This is most apt to occur in bone conditions and in aneurysm.

Bones and Joints

Many patients with painful bones and joints, sometimes with considerable swelling, are sent to the roentgenologist for diagnosis, and frequently no bone lesion can be detected by the x-ray; this is especially true in the early stages of syphilis. In such cases the diagnosis must be made on general clinical and laboratory grounds. From the roentgenologic standpoint such cases may be confused with a bursitis or with the tearing loose of a tendon, hence a careful history is of value to the operator in making his interpretations, especially as it is well known that syphilitic tissues often react very severely to injury.

The bone lesions of congenital and acquired syphilis from the x-ray standpoint are quite the same, with the exception of the typical osteochondritis of the former. However, the congenital form shows a tendency to involve the diaphyses of long bones and to affect a large number of bones. In common with the majority of observers we have found periostitis to be the most

Fig. 142.—A young girl fell from a chair to the floor; within a few weeks a large swelling developed just below the elbow, which was at first thought by the surgeons to be sarcomatous, but the Roentgen rays showed periostitis, which was definitely syphilitic in character.

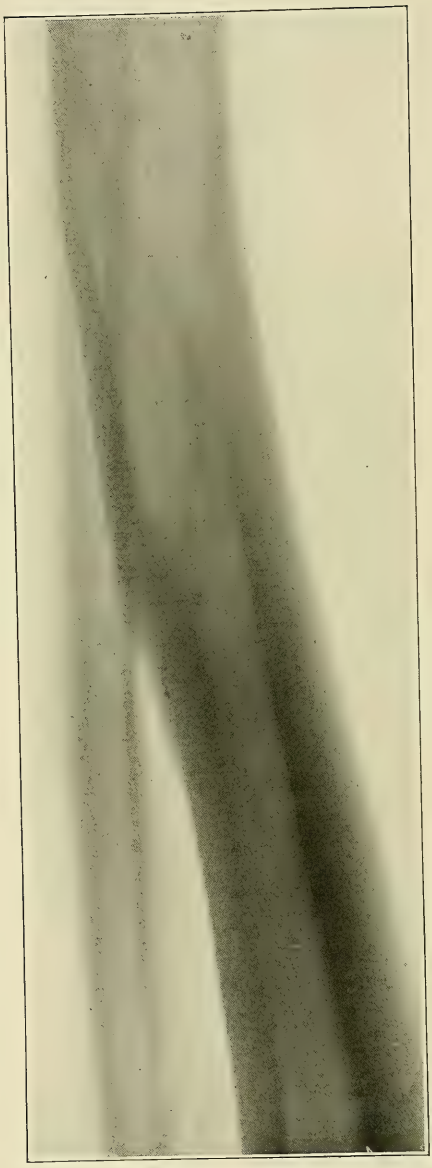

Fig. 143.—In syphilis the shaft of the bone is frequently thickened.

common bone lesion of acquired syphilis. To make sure that the condition is syphilitic we need other confirmatory evidence, for injury or tuberculosis may give a similar picture. However, in syphilis there is apt to be more than a single type of lesion; there may occur osteomyelitis, rarefying or productive ostitis, gummous infiltration or necrosis, or some other combination.

Ware[47] states that the whole pathologic process is to be regarded as an osteomyelitis, either in marrow beneath the periosteum or about the epiphyseal line of ossification.

The specific process may be gummous, sclerotic, purulent, or a combination of these three. The end results may be ostitis, necrosis, osteoporosis, sclerosis, sequestra formation, interference with growth and spontaneous fracture. Albers-Schonberg, Hahn,[48] Kohler and Ritter regard periostitis, eburnation and osteoporosis as typical of syphilis.

The participation of the periosteum in the pathologic process serves to exclude neoplasms. Tuberculosis may show translucency due to absorption and atrophy of bone, but never an increase in the shadow due to bone proliferation, and but seldom thickening of the periosteum. Any bone may be the seat of syphilitic inflammation and destruction. According to Keyes bones are affected in the following order of frequency: tibia, parietal, frontal, sternum, clavicle, ulna, femur, ribs, metacarpals, humerus, temporal, phalanges, fibula, maxillae, calcaneum, occipital, patella, ilium, radius, metatarsal, tarsal, malar and scapula. Horsley[49] gives a somewhat similar order.

In order to describe the roentgenologic findings it is necessary to briefly recapitulate the pathologic conditions occurring in bones. Periostitis is an inflammation of the covering of the bones and in syphilis is always chronic. If ossification of the periosteum occurs, it is called osteoperiostitis. Syphilitic periostitis varies in intensity from the flat superficial type occurring during the earliest stages of syphilis, described by Taylor, and not demonstrable by the rays, to the most marked thickening, which gives rise to great deformity and often loss of function, if occurring in the neighborhood of joints. Normal periosteum is not visible on a rœntgenogram, hence any visible thickening, no matter how slight, is indicative of a pathologic process. Periostitis begins in the connective tissue as a perivascular round cell and

plasma cell infiltration. Usually the vessels around the Haversian canals participate, and as the process advances the newly formed cells act as osteoblasts, thus forming bony spicules.

Syphilitic periostitis must be differentiated from the type occurring in periosteal sarcoma, rickets, tuberculosis and injury. In syphilis the swelling often involves the whole circumference of the bone, and may show bone spicules, and is tapering in character, while in periosteal sarcoma the growth occurs only from one side, seldom shows bone spicules, except in ossifying sarcoma, and there is not the definite tapering appearance.

In rickets there is a uniform bending with a buttress of new bone along the concavity, the bone becomes flattened, and there is usually a broad band at the diaphyseal end that gives a characteristic picture.

Typical periostitis occurs only in the late stages of tuberculosis, and then in association with sequestra formation.

In periostitis due to injury the lesion is small, circumscribed and on one side only.

Ostitis is inflammation of the bone, and is either of the rarefying or condensing type. In the former absorption of the bony lamella takes place (osteolysis), while in the latter, portions of the marrow are converted into dense bone (eburnation). Horsley states that syphilitic ostitis is either rarefying or productive, the former being the first to appear, and being frequently followed by the latter. Rarefying ostitis occurs in other diseases than syphilis, but when accompanied by sclerosis, is characteristic of lues. Kermisson[50] agrees with this statement. Mallory states that the lesion starts as a mild inflammatory process; the fibroblasts which proliferate in the process of repair produce bone because they are derived from the osteal cells. The result is sclerosis within and periosteal thickening without. The lesion may be complicated by necrosis, due to the obliteration of the blood vessels (osteolysis), but where necrosis has not occurred, the new formation of bone takes place. This combination of erosion and new bone formation is fairly characteristic of syphilis.

Powers[51] says that ostitis must be differentiated from myeloma; in the latter condition the growth is uniform, the bone gradually becomes expanded, and there is evidence of interference with the circulation, that is, the cutaneous veins are en-

gorged and there is edema below the tumor. Early cases are difficult to differentiate by x-ray examination, but late myelomata show absorption of bone in and around the growth without any thickening in the periosteum which is so characteristic of syphilis.

Osteomyelitis is a condition in which the marrow is primarily attacked and the trabeculae and cortex are at first but slightly invaded. The process may spread extensively in the marrow be-

Fig. 144.—This illustration portrays the syphilis of the bones of the hands and fingers in a young child suffering from congenital syphilis.

fore the cortex is involved. Adami says that it is rare in the long bones, to which statement we take exception, but that it is occasionally met with in the phalanges and in the diplöe of the cranial bones. Powers believes that osteomyelitis, strictly speaking, includes every form of osseous inflammation from a simple periostitis to the result of the most acute infection with pyogenic microorganisms. Fitzwilliams[52] agrees with this and thinks that the whole thickness of the bone is attacked and replaced more or less completely with gummous tissue, which may eventually de-

stroy the continuity of the structure without necessarily discharging through the skin. The radiogram of a pure osteomyelitis is not characteristic in syphilis and will not serve to establish a diagnosis of that disease. It will show rarefaction or destruction of the marrow, later also the bone cortex with possible sequestrum formation.

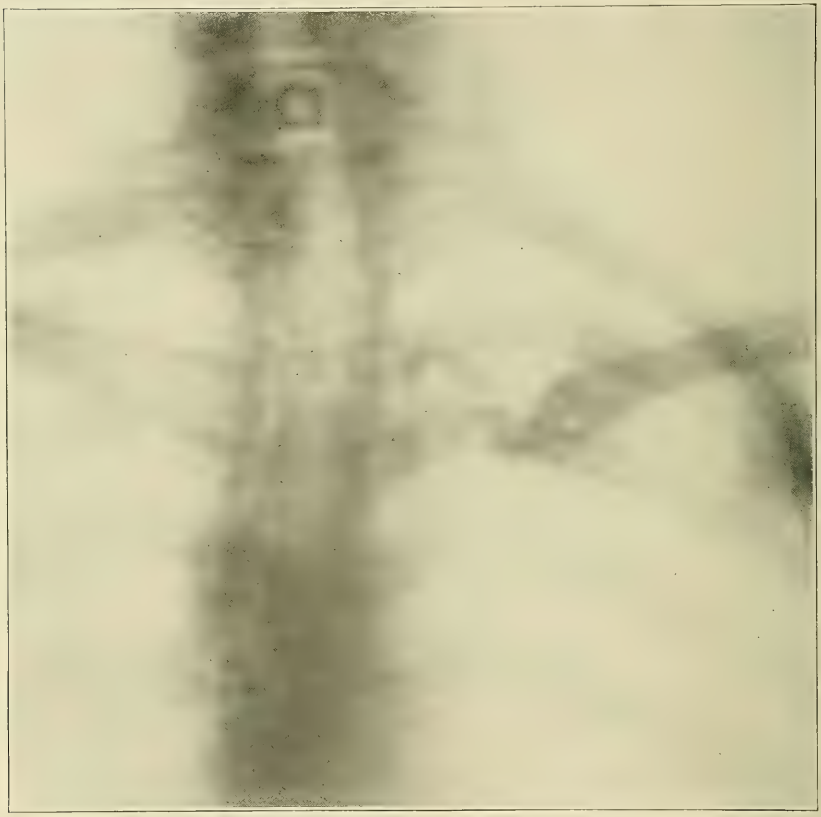

Fig. 145.—The head of the clavicle may show complete absorption.

Osteochondritis involves both the bone and cartilage. Both Taylor[53] and Post[54] consider this the earliest and most characteristic bone lesion of congenital syphilis. The former gives the following pictures as being typical: The affection results from interference with the nutrition of the bone and presents three stages. In the first stage there is hyperplasia of the cartilage cells

resulting in thickening and irregularities. In the second stage there is an increase of the condition just described plus calcification of the cartilage, forming bony papillae, that is to say there is an irregular osteogenesis, premature in some regions, but delayed in others. In the third stage the proliferation of cartilage cells and lime infiltration is excessive. In the layers adjoining the bone there are nonnucleated cells, spindle-shaped cells and granular detritis resulting in general enlargement of the epiphyses with thickening of the periosteum and perichondrium. Degenerative changes are apt to occur.

J. R. Kuth[57] states the earliest radiographic changes in osteochondritis are best seen in the fetus or a child at birth or at most a few weeks after. The longer the child lives the less distinct the changes becomes until they finally disappear.

When present typically the radiogram shows a heavy broad homogeneous irregularly jagged band-like shadow at the epiphyseal-diaphyseal line. Beneath this there is a band showing increased penetration by the rays, (delayed osteogenesis of Taylor) which gives the impression of a break in the continuity of the shaft, below this the shaft is seen to continue. There is also thickening of the periosteum or the appearance as though the bone were lifted away from the bone cortex. Later gummous degeneration or osteomyelitis may occur. Partial or total epiphyseolysis may also be seen; the separated edges showing very ragged. These changes are followed by a pronounced atrophy. (Postluetic atrophy of Holzknecht.)

Rickets with which this condition might be confused shows in the radiogram a cup-shaped epiphysis also there is an absence of shadow-casting lime salts at the epiphyseo-diaphyseal junction.

Adami states that the bone lesion of syphilis is really a specific osteochondritis, and that the line of calcification is broader than normal and more irregular. Fitzwilliams emphasizes the fact that perichondritis of the laryngeal cartilages may rapidly prove fatal by obstructing respiration, the symptoms resembling laryngeal diphtheria minus membrane and bacteria.

Synovitis is an inflammation of the synovial membranes, and does not merit discussion at this point, although we agree with Ware that it is usually due to an extension of the syphilitic process from the epiphyses.

Fig. 146.—Syphilitic periostitis is usually characteristic, although it may be simulated by tuberculosis in rare instances.

Fig. 147.—A late osteochondroarthritis may closely resemble a so-called Charcot's joint. Note the marked periostitis.

Gummata are gelatinous or fibro-gelatinous foci; often of a purulent character, in which the bone becomes necrotic. The bone in the neighborhood of a healing lesion often shows eburnation. Kermisson thinks that they are rather difficult to differen-

Fig. 148.—In a so-called Charcot's hip, there was periostitis of the descending ramus of the ischium.

tiate from nonluetic osteomyelitis; sequestra formation is rather rare.

Charcot's joint is a chondro-osteolysis usually associated with tabes dorsalis, although it may occur where there is no demonstrable cord lesion. The destruction of the cartilages and of the

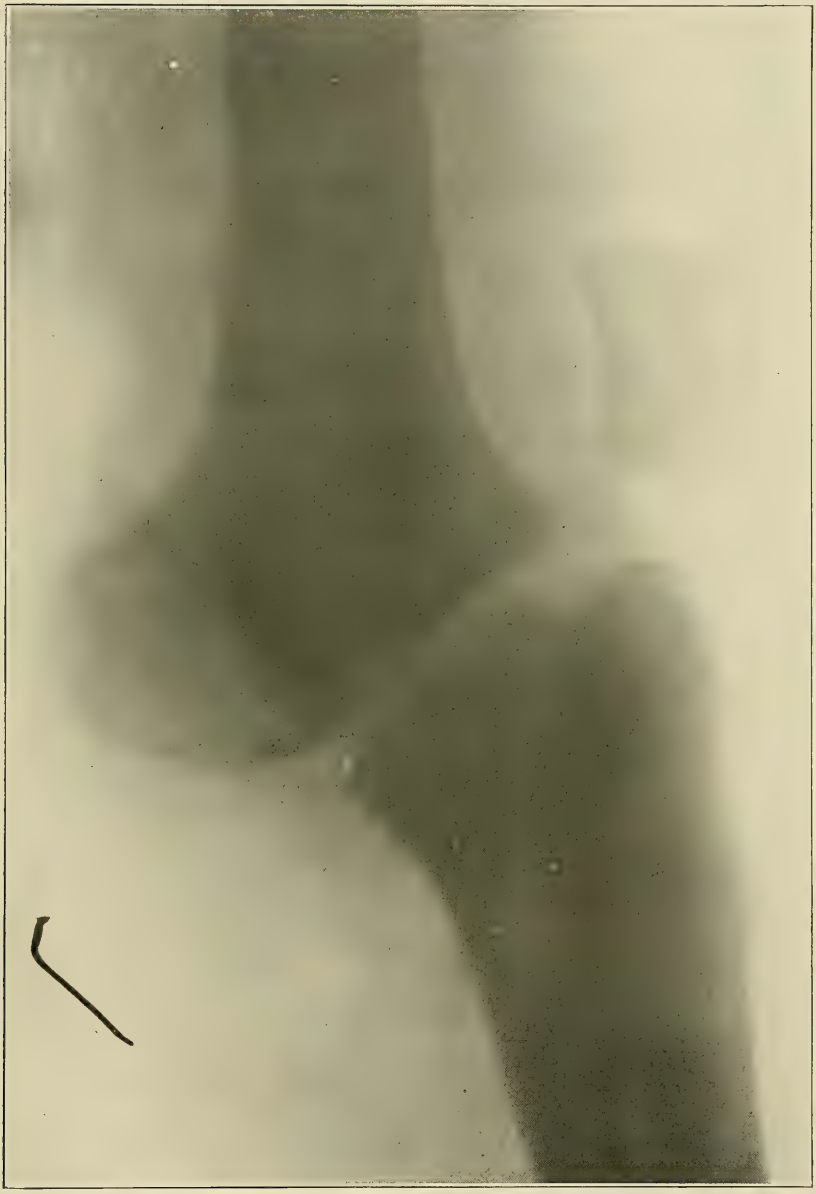

Fig. 149.—In this advanced Charcot joint, occurring in a tabetic, there were definite syphilitic changes in the periosteum.

head of the bone may be so complete as to give rise to luxation or a flail joint. Effusion is usually present. The roentgenogram is rather characteristic and shows destruction of the head of the bone and of the cartilage, often with some misplaced fragments. Inasmuch as in a study of about a dozen cases we have found periostitis and other evidences of syphilis, and inasmuch as we have found a similar picture in at least one active case of syphilis where there was no cord lesion we feel that in the majority of instances the so-called Charcot's joint is a true syphilitic lesion due to the local action of the treponema. However, Baetjer states that the condition may arise with syringomyelia.

Spine

By most authors the spine is not mentioned as the site of syphilitic processes; however, in the past few years considerable literature has accumulated upon this subject. The cervical region is more frequently affected than is any other. Any portion, either the bodies, or the processes may be affected. Bine[55] has reported an interesting case with destruction of the odontoid process and intervertebral substance. The clinical course may be very rapid. It is difficult to tell from tuberculosis by the x-ray.

Other articles of interest are those of Bodin,[56] Kuth,[57] Kienbock,[58] Axhausen,[59] Roices,[60] Lydstrom,[61] Tedonot and Vennes,[62] Straub,[63] Rolliston and Taylor,[64] Joachimsthal,[65] Touissant,[66] Milian,[67] Bonnea,[68] Rizzi,[69] Montot and Beaujeu,[70] Jourdson,[71] Renault,[72] Von Niessen,[73] Tikhonovitch,[74] Bengold,[75] Saunders,[76] Engel,[77] and Bernard, Letreat and Solomon.[78]

The Aorta and Aneurysms

It is now well realized that syphilis is a frequent cause of aortitis, and that this lesion may result in either a dilated aorta or in aneurysm. Care should always be taken to distinguish between dilatations and aneurysm, the latter term applying only to sacculated lesions.

One of the best accounts of the value of the x-ray in the diagnosis of dilated aorta is that of Longcope,[79] from whom we shall quote verbatim:

"Of all the methods of physical diagnosis, however, to de-

Fig. 150.—Aneurysms of the arch frequently run well into the neck.

termine whether or not dilatation exists, the x-ray is the most valuable. The orthodiagraph, as pointed out by Vaquez,[80] gives undoubtedly a more accurate picture than the skiagram or fluoroscopic examination. * * * Fluoroscopy seems indispensable.

Examinations have been made with the patient in the prone position, and lately it has seemed useful to examine the patient first with the screen on the chest and then on the back. In the latter

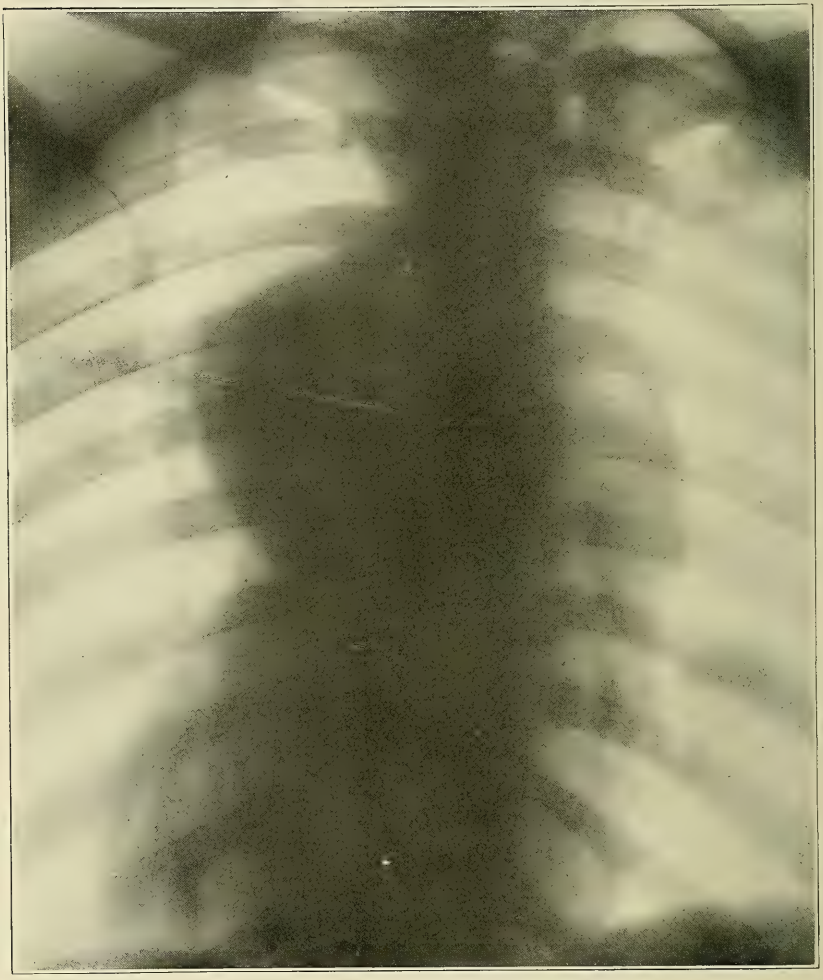

Fig. 151.—A rear view of an aneurysm of the arch.

position, when the patient lies on his face, the shadow of the heart is not very clear, but the outline of the arch and descending aorta is very distinct and can be studied with much advantage. The details of the changes in the size and shape of

Fig. 152.—Even small aneurysms cast a definite shadow. This is one of the descending arch.

the aortic shadow when dilatation exists have been well discussed by Vaquez, and indeed are familiar. The shadow of the normal aorta as seen on the fluoroscopic screen, or in the skiagram lies

Fig. 153.—Aneurysms may grow to a great size. In this instance the patient died because of pressure, not because of rupture.

in its first portion behind the sternum, but at the arch where it curves rather sharply backwards and to the left, there is a well-defined rounded knob, seen to the left of the sternum and opposite the second dorsal vertebra. According to the age of the patient and position of the heart, the shadow may show certain

variations, none of which can be confounded with definite dilatation.

"The commonest changes that I have observed in dilatation are as follows:

"First, the aortic shadow as it ascends from the heart shadow is widened so that it projects in a curved line beyond the sternum and reaches to or extends beyond the curved right border of the heart. In most instances the outer shadow is regular, but it may show slight protrusions or bulgings. To the left the normal shadow is broadened. There may, too, be localized irregularities on this outline. In a second group there are alterations of a more or less prominent character in the shadow of the aortic knob, but since this represents the arch, it is unaffected unless the dilatation reaches that far. The commonest abnormality which has been observed is a general enlargement with loss of the well-defined knob shape, instead of which there is a crescentric curve towards the left. In other cases the knob may be enlarged, and its form more prominent than normal. Finally in a third group the aortic shadow appears more or less as a truncated cone with rounded apex and broad base resting on and fusing with the cardiac shadow. In such instances the normal aortic knob is obscured.

"In any instances * * * there may be above the aortic shadow a pyramidal-shaped shadow with base upwards, and beneath the clavicles. This often corresponds to dullness which is obtained beneath the sternal ends of the clavicles * * * "

Thoracic aneurysms can be easily recognized by the x-ray, even though they are not found on physical examination. At the Freedmen's Hospital we have established the diagnosis in many instances where the clinician was by no means sure of the trouble. Aneurysm shows as a mass in the mediastinum. Lesions of the ascending arch show to the right of the sternum, lesions of the transverse arch extend upwards, while those of the descending arch usually show to the left. Of course in the case of large growths it may be difficult to say just what the point of origin was. It is always important to flouroscope a patient with a suspected aneurysm, for any mass in the mediastinum may simulate the condition unless the expansile pulsation be noted; even then a very vascular sarcoma may show some pulsation, but no other condition can possibly be confused.

On the other hand the x-ray not infrequently totally fails to

reveal the presence of an abdominal aneurysm, especially if it be behind the liver. For further information the articles of Baetjer[81] and Carman[82] may be consulted.

Fig. 154.—In syphilis of the lung there is frequently a diffuse sclerosis of an entire lower lobe. Also note the mediastinal thickening. (Private collection of Dr. Van Sweringen.)

The Lungs

Most radiologists admit that it is difficult for them to distinguish syphilitic lesions of the lungs, for they believe that the shadows cast are not pathognomonic. Watkins[83] has recently

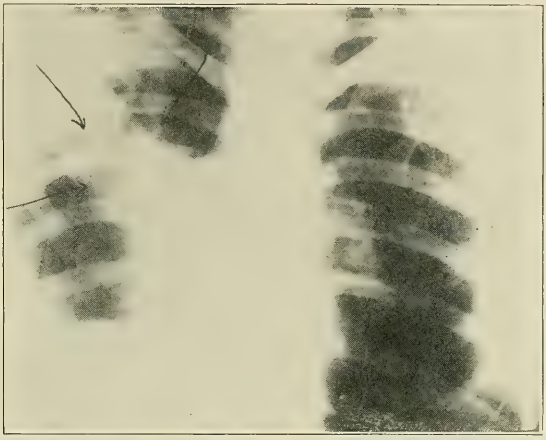

Fig. 155.—Dense sclerosis due to syphilis. (Collection of Dr. W. Warner Watkins.)

Fig. 156.—Diffuse sclerosis due to syphilis. (Collection of Dr. W. Warner Watkins.)

made a study of the condition and has reached the following conclusions: Syphilis tends to invade the lower and middle lobes, it tends to involve the tissues at the hilum first, so that the densest shadow is there, and the shadows do not bear a dis-

tinct relation to the bronchi, as in tuberculosis. At the edges they have a ragged, worm-eaten appearance. In other instances the lung is evenly speckled, or there are lance-like radiations of dense fibrous tissue. With the majority of these conclusions we are prepared to agree, although we should also like to mention still another variety, where there is a very dense shadow through the mediastinum and in the adjoining portions of the lungs. The following conditions must be differentiated: cancer, which gives a localized shadow with a sharp margin, except in the case of some infiltrating carcinomata, which can not be distinguished;

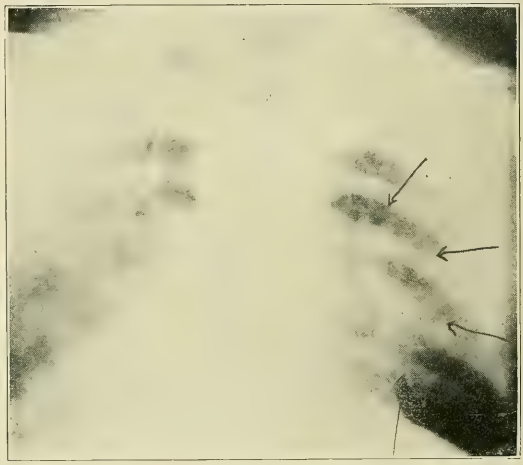

Fig. 157.—Syphilitic consolidation, involving portion of lobe. Note the irregular edge and pointed projections. (Collection of Dr. W. Warner Watkins.)

pneumokoniosis, which presents great difficulty in diagnosis; unresolved pneumonia, which is likewise difficult to distinguish; tuberculosis, which tends to first invade the upper lobes or apices and which shows distinct shadows in relation to the bronchial tree.

Articles by Moore and Carman,[84] Callender,[85] Post,[86] Bauch[87] and Dunham[88] may be consulted.

The Stomach

There are four types of gastric syphilis, syphilitic gastritis, ulcer, tumor and diffuse infiltration. The first named condition

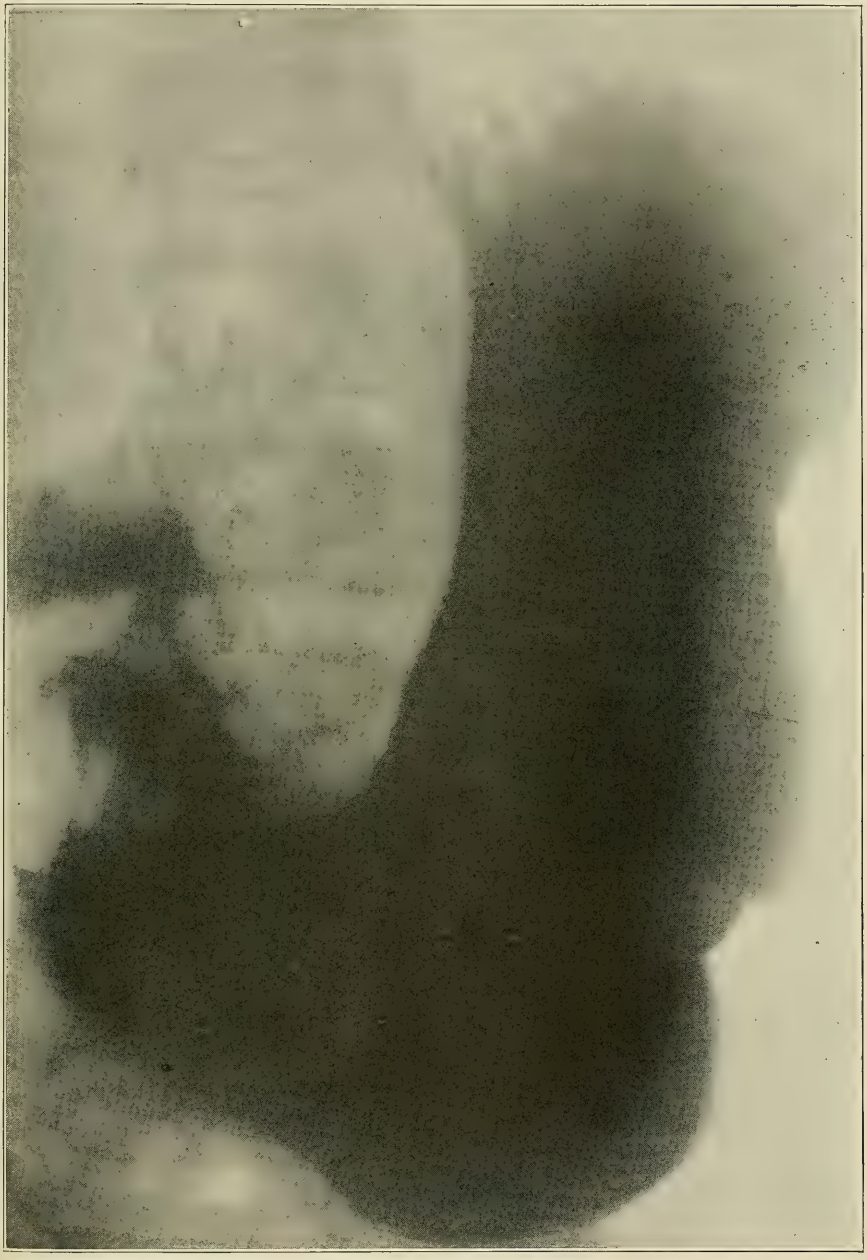

Fig. 158.—Large, ulcerated gumma, involving pyloric fourth of stomach, with partial obstruction. Patient, female, aged 52. (Collection of Dr. Frank Smithies.)

casts no shadow so need not be considered. Many syphilitic ulcers can not be distinguished from peptic ulcers, but in a fair number of instances one of the following findings will make the operator suspicious; multiplicity of ulcers, or absence of a niche,

Fig. 159.—Large gummous ulcerated infiltration of entire stomach wall with extensive tumor formation at the antrum and with stenosis. Patient, male, aged fifty-nine. (Collection of Dr. Frank Smithies.)

accessory pocket or typical incisura. However, we should caution against making a positive diagnosis on the x-ray findings alone; they are simply valuable confirmatory signs. Tumors are hardly

characteristic except in one particular: it is unusual for a patient with a large cancer to be in as good physical condition as are the majority of patients with hypertrophic luetic lesions. Diffuse syphilitic infiltration can not be distinguished from a diffuse fibrosis due to other causes.

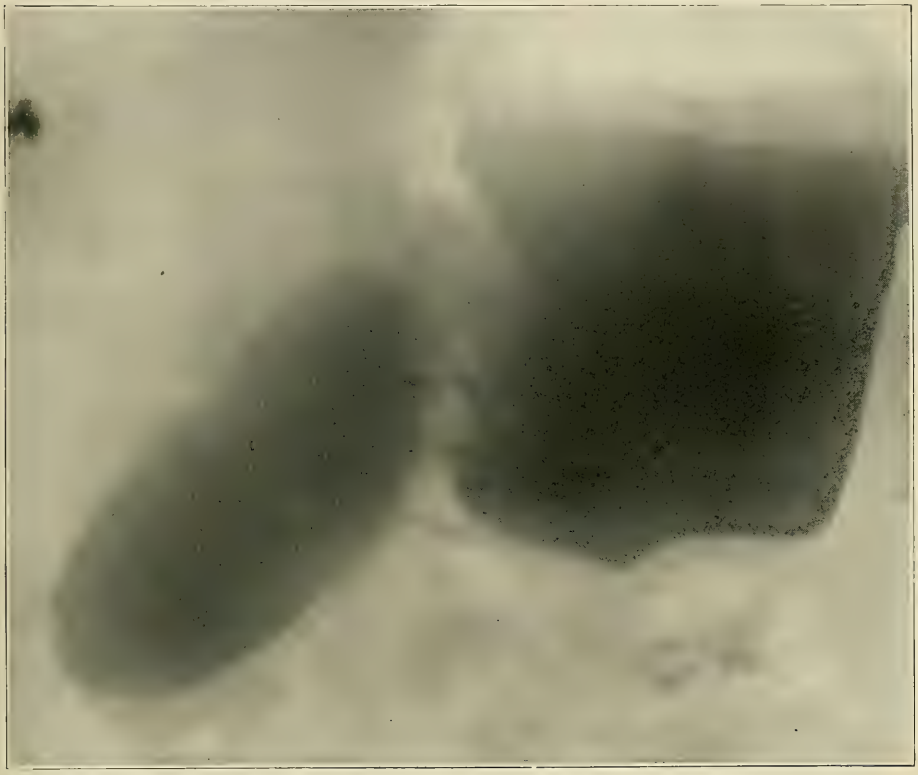

Fig. 160.—Gummous ulcer, with hourglass. Patient, male, aged forty-one. (Collection of Dr. Frank Smithies.)

Articles by McNeil,[89] Carman,[90] Eustermann,[91] Downes and Lewald,[92] Christie,[93] Mills[94] and Morgan[95] are well worthy of reading.

The Intestines

In the intestines the same syphilitic processes may occur as in the stomach. The literature is surprisingly silent as to the x-ray

findings. It would seem that multiplicity of ulcers might make one suspicious. Mortimer[96] has recently reported a case of syphilis of the duodenum, together with an x-ray picture.

Nervous System

As yet there have been no reports as to the possibility of diagnosing certain types of cerebral syphilis by the roentgen rays. It is possible that a large solitary gumma might cast a shadow, just as an occasional cerebral tumor will do.

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CHAPTER XXII

PROGNOSIS

After reading many articles upon the prognosis of acquired syphilis one seems justified in summing up the question as to individual prognosis in the following words: Verily the fate of the syphilitic is doubtful. As late as 1910 we find as well-trained an observer as Keyes[1] writing: "So convinced am I of the benignancy of well-managed syphilis that I always venture to prophesy to a patient, when he puts himself in my hands, that if he will take proper care of himself he need only expect a trifling inconvenience from the disease, and that at the end of his three or four years of treatment he will have to confess that his fear of the disease has been by far its greatest inconvenience. * * * I have yet to see the syphilitic who, having taken this three-fold care of himself, came to any great harm. But syphilitics are as human as the rest of us, and less than half of them continue to lead prudent lives."

More recently Warthin[2] has published an article in which we find the following words: "Likewise in the case of syphilis, therapeutic optimism has in recent years received severe blows at the hands of the pathologist. The frequency of latent syphilis of the heart, aorta, and central nervous system, the demonstration of spirochetes in conditions (paresis, tabes, etc.) until very recently regarded as parasyphilitic in nature and etiology, thus proving these conditions to be still active infections, have somewhat shaken clinical optimism. Cures once promised after a year of active treatment have passed through the two-, three-, and five-year limit, and now some clinicians are advising the syphilitic to take interval treatment over a period of many years or even throughout his lifetime if he will escape the uncertain chances facing everyone who acquires the disease. The wave of therapeutic optimism excited by salvarsan and the negative Wassermann reaction even now is subsiding.

"It has been my experience as a pathologist to become very pessimistic as to the curative effects of any of the present-day

methods of treating syphilis. Before the spirochete became an absolute pathognostic sign of the presence of the disease, certain myocardial, aortic and testicular changes were recognized by the pathologist as well-nigh proof positive of syphilis. The practically constant occurrence of these changes in the bodies of cases of clinically cured syphilis gave the pathologist good reason to believe that he was dealing with a still active process, although he had no means of proving this. The pathologist's judgment of these conditions is now confirmed by the demonstration of the spirochete of syphilis in such lesions. * * *

"In all of these forty-one patients the lesions of active syphilis were practically of the same nature, whether in cases that had been treated, or were being actively treated, or had received no treatment at all. Active syphilitic lesions were found in the heart in thirty-six cases, in the aorta in thirty-two, in the testes in thirty-one, in the liver in four, in the adrenals in six, in the spleen in one case, pancreas in six cases, and central nervous system in five cases. * * *

"The therapeutic lesson is evident. Promises of cure within definite time limits can never safely be made, and our advice as to treatment must include the possibility of treatment extended over many years. The syphilitic must be treated as a germ carrier. The latency of the infection seems to be the same in many untreated cases as in those receiving very good treatment. Our present-day treatment seems only to succeed in rendering the infection latent rather than in curing it. Clinical cures may not be cures at all, as shown by the autopsy. From the standpoint of eugenics it may also be said that absence of symptoms, or even the history of infection, and negative Wassermann reaction can not be taken as an absolute criterion of freedom from latent syphilis."

As is usually the case we find the clinician and the pathologist at odds over the question of complete cure. Yet this is but natural, for the clinical man naturally thinks of the patients who do not show any symptoms for many years, and the pathologist can not help recalling the fact that he has indisputable evidence that in many instances the disease is far from being cured.

The statistical evidence upon syphilis is necessarily very incomplete because until within a few years the great prevalence of syphilis, as well as many of its ravages, has not been recognized. Keyes quotes some figures in his article as follows: "Mathes, of Jena, studied the cause of death in one hundred and sixty hospital syphilitics and found that 15 per cent surely and 22 per cent probably, died as a result of the disease. It is to be noted that these statistics were obtained among hospital patients, i.e., among patients of the lower classes.

"At the other end of the scale insurance statistics may be quoted. Byron Bramwell estimates that 75 per cent of the syphilitics insured in the Scottish Widows' Fund died of their disease, while Blaschko estimates from the statistics of the Victoria Company that 26 per cent to 33 per cent of syphilitics die of their disease; constituting 6 per cent of the total mortality of this company. * * *

"As an interesting corollary it follows that the average abbreviation of life by syphilis is slight; viz., one year and four months, according to Bramwell; four years according to Blaschko."

In an earlier chapter in this book it was estimated that syphilis costs the United States over twenty-six thousand deaths each year. Leredde[3] has given almost the same figures for France. Also it has been pointed out that the various insurance statistics as quoted by Brockbank[4] show that the average syphilitic has a mortality of 33 per cent above expectations.

When we recall the immense prevalence of syphilis we must be reminded of the fact that syphilis would not be so prevalent were there not very many active cases at large.

We know that but comparatively few persons die from what the census reports, and the doctors' certificates, call syphilis, but die they must as the results of syphilitic infection. Probably the majority of the deaths are directly due to syphilitic involvement of the heart and aorta and of the central nervous system. Thanks to the labors of the pathologists we know very definitely that the majority of all infected persons develop cardiovascular changes, and many of these unquestionably end in death, although by far the larger number cause but little disturbance. Elsner[5] states that from 15 to 20 per cent of all syphilitic patients

in the past have developed lesions of the central nervous system. Taken all in all we must conclude that syphilis is a serious infection, and that it has caused many deaths.

But to turn to the standpoint of individual prognosis, what are we to say? What can we tell the individual patient? Reasoner[6] believes that about 50 per cent of the cases that are intensively treated within the first three weeks of the development of the chancre remain well. Personally I think these figures high, for I have seen one relapse in a case that had more than fulfilled all of the army criteria. And yet there can be no doubt but that many of the cases that are thoroughly well treated do become cured, for there is a rapidly growing list of reinfections in the literature. It is possible that a fair percentage of the cases in the early secondary period are permanently cured: I think that I have had several of these. However, after the infection has lasted more than three months, it is very doubtful whether a permanent cure can be obtained.

But even if a case be not cured, there can be no doubt but that early efficient treatment greatly decreases the chance for a relapse. As bearing upon this point the figures of both Neisser[7] and Fournier are very striking.

TERTIARY SYPHILITICS RECEIVED	PRIVATE MATERIAL	CLINIC AND POLY-CLINIC UNTIL END OF 1893	CLINIC AND POLY-CLINIC 1894 AND 1895.
No treatment, or but one.	35.4% males. 66.6% females.	72.3% males. 80.4% females.	68.8% males. 76.8% females.
One course	23.3% males. 16.5% females.	20.44% males. 14.2% females.	14.0% males. 16.0% females.
Two or three courses.	29.3% males. 8.5% females.	3.5% males. 2.4% females.	8.9% males. 5.8% females.
Four or more courses.	12.0% males. 8.4% females.	3.4% males. 2.8% females.	8.9% males. 1.4% females.

It is plainly evident that cases which have been properly treated are in less danger of developing severe late lesions.

The next question that arises is what prognostic importance can be drawn from the type of early lesion. Many have thought that extragenital chancres were the most apt to result disastrously. Within the past few years White[8] has lent his authority

to this point of view. Personally I can not believe it, for it seems to me that the all important question is that of the strain of the infecting organism, a point to which I shall shortly return. After a thorough study of a large number of cases Fournier[9] has decided that the type of lesion, be it chancre, mucous patch, or secondary eruption, from which syphilis was acquired has absolutely no influence upon the course of the disease. Likewise neither the incubation period nor the early cutaneous manifestations give an index as to the subsequent course of the infection. In regard to the late manifestations he gives the following figures:

"Out of a total of 1,664 cases, including all kinds of tertiary lesions I have found the antecedents as follows:

Benign or very mild secondaries,	1,424 times
Secondaries of average severity,	131 "
Severe secondaries,	45 "
Early malignant syphilis,	64 "

"Deducting the last group of cases, which do not bear on the question, we arrive at the following conclusions:

"1. That tertiary manifestations may follow all forms of secondary, benign, medium, or severe.

"2. That in the great majority of cases they follow secondary syphilis of a benign character.

"In round figures, out of ten tertiary lesions there are nine which follow originally benign syphilis, as against one which is preceded by secondary syphilis of average or severe nature."

White[10] has clearly shown that the majority of cases of tabes and of cerebrospinal syphilis as well, develop in those who have shown no recurrent cutaneous manifestations. In the majority of my cases of severe visceral manifestations I have noted that either the cutaneous manifestations were absent or mild during the early course of the disease, and that the late cutaneous lesions were usually very mild or totally lacking.

This point has probably been cleared up by the demonstration by Nichols[11] and Reasoner[12] that there are different strains of treponemata, strains which have an affinity for special tissues. This point is elucidated at length by Reasoner in his chapter upon Pathology. Hough and Reasoner have both told me that clinically they have usually observed syphilis of the central nerv-

ous system to follow upon a small, indurated chancre. It is highly probable that the future course of syphilis depends almost entirely upon the nature of the infecting organism, and that at some future date it will be incumbent upon the syphilologist to determine just what the nature of the strain is, so that the patient can be more carefully watched.

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[11]Nichols: Jour. Am. Med. Assn., 1914, lxiii, 466.
[12]Reasoner: Jour. Am. Med. Assn., 1916, lxvii, 1799.

CHAPTER XXIII

PROPHYLAXIS

As Pusey[1] has well pointed out we now have at our disposal complete data as to syphilis: we know how the disease is acquired and hence it should be easy to prevent were it not for the fact that it is intimately connected with the social problem. The sexual instinct, next to that of hunger, is the strongest that man possesses, and at the present time it is useless to try to prevent sexual intercourse outside of the marriage bed. In the next place the great majority of persons, certainly practically all Americans, absolutely object to any laws or regulations that might control their sexual habits, and lastly once a person has syphilis he is secretive about it. No matter how unpleasant certain of these facts may be to the person who is trying to control syphilis, if he is honest he must admit all of them. And yet there is much that we can do to prevent the spread of syphilis, and that this is absolutely necessary is now universally admitted. As the author has attempted to point out in the preceding chapters, syphilis is common, and it attacks both the innocent and the guilty; in addition it is an extremely important economic problem.

The question of prevention may be treated under four heads, first that of legislation, second that of education, third that of personal prophylaxis, and fourth that of shortening the contagious period.

Legislation

While it must be admitted that no laws can be enforced for which a people is not ripe, still legislation may do much good. We shall now consider various enactments that have been considered.

Segregation.—It is universally conceded that it is impossible to segregate the syphilitic, although to do so would stamp out the disease. In the first place there are too many syphilitics, and too many in high places. In the next place segregation to be effec-

tive might require long detention, and would seriously handicap any community that tried it. Then, too, there is entirely too serious objection to it on the part of the community.

Control of Prostitutes.—At the onset it should be clearly understood that clandestine prostitution is far and away the largest class, and that comparatively little syphilis is acquired in the houses of prostitution. Less than 10 per cent of my cases in men have been derived from the regular houses of prostitution, but the vast majority from some girl who is selling her body "as a side line." Fournier[2] believes strongly that a prostitute, with active syphilitic lesions should not be permitted to ply her trade, and personally I feel with him that such an individual should be segregated. Von Düring, as quoted by Osler and Churchman,[3] opposes state regulation on the following grounds: "(1) The medical supervision is necessarily incomplete and therefore gives a false sense of security. (2) The industry is one which leads to much misery and the state should have no hand in it. (3) The number of prostitutes in a community can not even be estimated approximately; the greater part of prostitution is clandestine; and for these reasons it is absurd to talk of regulating it. (4) State regulation is contrary to the Constitution of the Governments which forbid pandering. (5) There is no need for brothels; this is proved by the fact that they are actually diminishing in number in most of the continental cities; and that at best the inmates of them represent a very small fraction of the total prostitution of a community. (6) Brothels are a danger to the state. They are morally unsound, as enticing to youth and teaching that illegitimate intercourse is safe. They offer allurements particularly to unripe youths and to the intoxicated. They mean slavery and a most dreadful existence for the inmates; and they are the breeding places for sexual perversions. They do not clear the streets, as is proved by the small percentage of the total prostitution of a community living in them. (7) Examination of prostitutes for venereal diseases is no function of the police; and it is most unjust, because it includes only the women. (8) Almost everyone who is well informed on the subject is against regulation. (9) State regulation, after a fair trial, has done practically nothing in diminishing the occurrence of venereal disease; it has been a practical failure. (10) To these arguments may be

added that of Josephine Butler, the famous English abolitionist: morality comes before every other consideration; hygiene only comes in the second place; 'if the safeguard were as real as it is fallacious it would in no way render regulation legitimate.'" Fortunately it is universally conceded that the state control of prostitution is by no means an important factor.

Punishment for Willful Transmission of Syphilis.—There can be no doubt but that some individuals who have acquired syphilis will deliberately expose others to the infection. In some instances this is done simply because of an absolute lack of moral decency, in other cases the unfortunate victim is determined to make others suffer. Dr. Hough of Washington, has told me of a trained nurse who acquired syphilis, and who vowed that she would spread it to every man that she possibly could. I have known of two instances where a man deliberately infected his wife, and later bragged concerning it. There can be no doubt but that such persons should be punished and punished severely.

Notification.—As regards the reporting of cases of venereal disease to the local authorities, there has been much discussion pro and con. The majority of hygienists are in favor of it, and the majority of men who treat such cases are bitterly opposed to it, feeling that it will drive the patients into hands of the quacks. Pusey[1] states strongly that the first requisite is to enjoy the confidence of the patient and to gain his cooperation, and that if the case must be reported this cooperation will be lost. Now this attitude seems to me to apply very nicely to the better class of patients, but it should always be remembered that the largest class of syphilitics is that attending the free clinics. All records show how poor their attendance is, and that in a large percentage of cases but one visit is made. Then, too, we all know how frequently the poor child with congenital lues is not brought for treatment for a disease for which it is in no way responsible. In other words there is a very large class of persons who will not take treatment. It is true that the recent English[4] commission has decided against notification, but the laws passed by the government of Western Australia appear model to me. According to the editorial in the *Journal of the American Medical Association:*[5] "It is based on the principle of controlling the venereal diseases by attending to their treatment until after they have

passed the contagious stage." But it goes much farther in this direction than any other act thus put into force. It does not simply offer facilities for treatment; it operates on the assumption that, for the good of the community, the person with venereal disease must submit to treatment until he is free from contagion, and it proposes to see that he does this.

"On developing a venereal disease, a person, within three days, must go to a regularly qualified practitioner for treatment. If he fails to seek treatment immediately he will be fined £20 or imprisoned. The physician must report to the health officials the age and sex of the patient and a diagnosis of his condition, but not the name or address. The patient is to return for treatment at least once a month; penalty for failure £20 or imprisonment. If he remains away from treatment for six weeks the physician under heavy penalty, must notify the health authorities, giving this time the patient's name and address, and the health authorities must bring the patient into court and compel him to have treatment. The patient may change his physician, but on doing this must disclose the name of his previous physician, who must be notified by the second physician that the patient is now under treatment by the latter. Treatment must be continued until the patient can obtain a satisfactory certificate of cure; penalty for failure £50 or imprisonment. The health boards have the authority to apprehend any person suspected of having a venereal disease which is not being treated, and to compel him to submit to examination by qualified physicians and to obtain a certificate of health, or to submit to treatment until such a certificate can be obtained.

"The measure takes ample precaution to prevent the treatment of venereal diseases by any other person than a qualified physician. It stops absolutely the advertising, the circulation or the sale of medicines intended for the venereal diseases, or of literature bearing in any way on their treatment. An important provision of the act looks to the protection of the secret of the patients by making private all legal procedures which have to do with the enforcement of the provisions of the act. Newspapers are prohibited under heavy penalties from publishing any reference to such legal proceedings. Every provision of the act is guarded by heavy penalties. It is evidently intended that

it shall be enforced, and that infringement of it in any particular shall be an offense which nobody will commit lightly. * * *

"Western Australia, before any body else, has taken the two essential steps towards the solution of the venereal problem. First it has recognized the importance of universal, prompt treatment of venereal diseases as the most efficient measure of their control. Secondly it has the wisdom and—what is unique—the courage to make laws compelling venereal patients to have treatment. * * * At the same time it is a law which has not the objections of notification. * * * But it wastes no great amount of sympathy on the miscreant who is indifferent to his duties in getting himself cured."

Control of Liquor.—It is generally recognized that the sale of alcoholics, at least of too much alcohol, is intimately connected with the question of the prevention of syphilis. It is an undoubted fact that many cases of syphilis are contracted by those under the influence of liquor. As Osler wisely quotes: "Sine Baccho friget Venus;" "Der schlimmste Kuppler ist eben der Alcohol;" "Aus der zwei V, Vinum und Venus, entsteht ein grosses W (Weh)." In other words any legislation looking to the limitation of sale of alcohol will also be a step towards the prevention of syphilis.

Control of Charlatans.—Many of the daily papers carry advertisements of medicines that are supposed to cure venereal disease, all that the patient has to do is to make his own diagnosis and to buy some drug over the drug counter. Also there are many self-styled specialists in "The Private Diseases of Men and of Women" who mostly are totally ignorant. Both of these dangers would cease to exist were it not for their advertisements, and such advertisements could legally be forbidden.

Better Sanitation.—If the poorer class were better housed, better fed, and had more opportunity for harmless amusements, there would undoubtedly be less venereal disease among them. In other words all true sociologic reforms are useful.

Education

There have been, of course, many good men and women who felt that proper education alone would almost suffice to prevent

venereal disease; they felt that if a young man knew the dangers that he was running into, he would abstain from illegitimate sexual intercourse. To some extent this may be true, but most of us know that many practicing physicians take grave risks along this line, and in the days gone by medical students were frequently notorious for their debauchery. While there is no doubt but that a proper realization of the risks would deter many a youth, still I gravely doubt that any great reduction in the prevalence of venereal disease could be effected in this way. It is highly probable that such instruction should come from the home, and it is almost certain that the public at large is awake to the danger, hence I do not feel that constant agitation is to be unreservedly recommended, fearing lest it make too many syphilophobiacs. At the same time the agitation should not be permitted to die down entirely, for even parents have short memories. There are many excellent pamphlets upon the market that point out the dangers attending the awakening of the sexual appetite.

Personal Prophylaxis

In regard to personal prophylaxis there are two points to be considered, first to keep from acquiring syphilis, and second to keep from giving it to others.

Continence.—Abstinence from sexual indulgence is perfectly compatible with good health. For some it is easy, for some it is difficult, but plenty of work and of exercise in the open frequently make it easier to abstain.

Preventives.—It is frequently objected that we should not recommend preventives, because when we do so we condone sexual irregularities. This objection is very true, but when one considers the number of innocent victims, usually estimated at about 20 per cent, he must accord respectful attention to the advocates of the condom or of a mercurial ointment. Metchnikoff and Roux have proved that if a man will rub his genitals with an ointment composed of twenty parts of calomel and forty parts of lanoline, within an hour after exposure, he is almost sure not to acquire syphilis. Reasoner's observation that soap will kill the treponema almost instantly suggests that soap and water may be another excellent prophylactic. Of course the smearing

of the penis with an ointment will not prevent the development of an intraurethral chancre, but this is a rare accident.

Circumcision probably has but little effect, although it has frequently been stated that the circumcised do not develop syphilis as often as those who have not undergone this little operation.

Syphilis and Marriage.—Pollitzer[6] has recently written on this subject, and his general treatment of the subject is followed, although I can not agree with certain of Pollitzer's views, considering that syphilis is not as easily cured as that writer seems to believe.

Forty years ago Fournier laid down certain principles as to the permissibility of marriage for syphilitics, namely, that if there had been three years of treatment with mercury and the iodides, beginning soon after the infection, and if then for a year or preferably for two there had been no lesions the syphilitic might marry.

Many happy marriages have followed the adoption of this rule, but in many instances both wife and posterity were infected. Within the past few years we have better criteria as to cure, although even yet we are by no means sure when a patient is permanently free from the disease. Probably syphilologists would pretty generally agree that a man might marry if he had been Wassermann negative for two years and if a provocative Wassermann and examination of the cerebrospinal fluid were also negative, provided that physical examination revealed no evidences of the disease.

With regard to the Wassermann positive or the Wassermann-fast cases, it should be remembered that many of them can be made Wassermann negative by prolonged and intensive treatment, but it is still a question whether relapse does not always take place, except perhaps in some of those due to lesions in the central nervous system which have had proper treatment. Personally I should hate a daughter of mine to marry any man who had been Wassermann-fast for any length of time. It is well known that about one-third of the paretics manage to infect their wives, and the percentage can hardly be less for others with cerebrospinal syphilis, hence we must be extremely cautious about permitting any one with lues of the central nervous system to marry. It is infinitely better to forbid it in all cases, or

at least to insist that the prospective wife be informed. Warthin's[7] paper on the intractability of syphilis to treatment should be read.

There are at least two reasons for not granting hasty permission to a syphilitic to marry: first, because he is not a good life insurance risk, and the family may be deprived of its breadwinner, and second, because both wife and possibly children may contract the disease, not a pleasant thing to have happen. Common sense and a realization of the dangers of infecting others must always be the guiding star when the physician is asked for his advice.

The syphilitic woman is much more apt to infect her husband when she has active lesions, but it must be remembered that treponemata have been found in the menstrual and leucorrheal discharges of women who showed no active lesions (Chase,[8] Graefenberg[9]) and by Gellhorn and Ehrenfest[10] in women with no apparent uterine lesions but with active syphilis, hence it is more than possible that the treponema may occasionally be found in the menstrual blood or cervical secretions of a Wasesrmann positive woman. The deductions are obvious, no woman should marry until Wassermann-free and then the same rule should be applied as for men.

In the chapter on congenital syphilis the risks and methods of infection of the child have been considered.

Much speculation has been indulged in and some work done in attempting to produce a vaccine against syphilis, but up to the present time no such substance has been produced, although we must admit that it is theoretically possible. As bearing on this point Zinsser, Hopkins and McBurney[11] and Kolmer, Broadwell and Matsunami[12] have shown that rabbits and sheep immunized with cultures of the treponema acquire some agglutinating powers of their sera and that some persons affected with syphilis have the same reaction. However, the former authors[13] state that immune sera exert practically no effect upon virulent organisms obtained directly from syphilitic lesions. Still later the same authors[14] have again confirmed this point.

The syphilitic patient must abstain from certain things which are dangerous to others. Until the Wassermann is negative, or while there are open lesions he should abstain from both sexual

intercourse and kissing. Separate dishes and separate linen should be used during this period, and he should certainly sleep alone. Also he should not loan his razor, or any article that goes in his mouth to others. It is probable that one, or at most two, injections of arsphenamine will render any syphilitic person free from the danger of transmitting the disease, but it is wise to lengthen the period of care until lesions have disappeared.

Shortening the Contagious Period

Most authorities are agreed that one of the most practical ways of lessening the prevalence of syphilis is by shortening the contagious period. This can readily be done by means of arsphenamine. The first essential in this form of prophylaxis is that arsphenamine shall be brought within the means of all individuals, and second that the diagnosis be made at once. It is a painful fact that in a large percentage of cases the diagnosis is made entirely too late. In order to correct this, better education of the physician is urgently demanded. At the present time syphilis is not well taught in the vast majority of medical schools. Every student should be taught that the dark-field illuminator is absolutely essential to the early diagnosis of syphilis. This and other points I[15] have discussed in a recent article, and more was said at the meeting of the Dermatological Section of the American Medical Association meeting in New York, 1917.

In regard to treatment one of the essentials is proper hospital and dispensary facilities. We all realize that many hospitals will not accept patients suffering from early syphilis. I feel strongly that every hospital should have a certain number of beds set aside for this purpose. In addition dispensary service must be better. The average clinic that treats syphilis is not adapted at all for the purpose. As regards this point Irvine[16] writes: "Treatment of all cases should be centralized in one clinic, one man seeing all cases, if possible, and directing treatment in each case; this personal contact does much to retain cases. Clinic should have own laboratory for Wassermann and spirochete examination and animals for experimental work. Clinic should have sufficient equipment of instruments. Clinic should have sufficient number of rooms so that each patient can be talked to and treated privately. Patients should under no circumstances be allowed to

see and carry around their own records. Clinic should have sufficient assistants and nurses so that each patient may be given enough time; this not only impresses the patient with the seriousness of the disease, but can not also fail to impress the student in contrast with the hurry-up order of things. Some arrangement should be in force whereby it is possible to administer salvarsan or neosalvarsan in infectious cases whether they have the money to pay for it or not. Records in most clinics show that many patients appear but once and they should not be allowed to leave without treatment. I believe that this is best done by charging a small profit to those who can afford it and using the surplus to pay for others. Clinic should have a sufficient number of beds at its disposal to confine infectious cases and do intraspinal work. Clinic should have adequate social service; from a public health standpoint no clinic can hope to do this work without this department. Patients should be furnished with literature apprising them of the seriousness of their disease and the importance of its treatment.'' Davis[17] has also written an excellent article on this subject.

Syphilis and the War

That syphilis always increases both during war time and during the period of five years following war, both among soldiers and among the civil populace, is a well-recognized fact. One has only to turn to the article of Melville[18] to see how great this increase has been in the various continental armies and in the American army. The present war has been no exception to this rule; every writer has emphasized the great increase in the number of cases of lues, both in the army and among the female portion of the population, both the wives of the soldiers and the loose women. Before the war started, the admissions for syphilis per 100,000 of the army were as follows: England (1908), 19.19; United States (1908), 28; Germany (1906), 4.7; Bavaria (1906), 3.6; Austria (1906), 19; Belgium (1906), 6.12; Italy (1902), 12.5. That these percentages have increased greatly may be proved by a brief consideration of the following facts: Pautrier[19] states that in 1916 there were 200,000 cases of acute syphilis along the French battle line alone, and Gaucher[20] reckons that in Paris the disease has increased 66.6 per cent. Balzer[21] be-

lieves that up to February, 1915, the Germans had 30,000 fresh cases in their Belgian army alone. I have been told by unimpeachable authority that syphilis has also greatly increased in the Italian army and also among the wives of the soldiers.

It would naturally follow that if the troops became infected a number of other persons would be put in immediate danger; that there have been a large number of extragenital chancres among the soldier associates seems to be proved by the statements of Cole[22] and Tullidge.[23] That syphilis has greatly increased among the prostitutes is commented upon by practically every writer on the subject. One of the saddest facts is that the soldier not infrequently returns home only to infect his wife, and that later we shall have a crop of congenital syphilitic children.

It has been found necessary not to debar men from the draft because of syphilis, unless the disease cause disability, such as would result from aortitis, serious bone disease, or lesions of the central nervous system. To this might well be added still another group, namely, those who have persistently recurring mucous patches, which as we well know are a grave source of danger. Of course, no man with active infectious lesions can safely be admitted to the training camps, but arsphenamine treatment will speedily render such lesions innocuous.

In our own cantonments there have been but a comparatively small number of fresh cases of venereal disease, although many more than there should be; here the infected men can and do receive satisfactory treatment from the onset; these men must not be discharged from duty because of their infection; if this were done there would unfortunately be many who would deliberately become infected in order that they might not have to go on the firing line, not knowing that the ultimate mortality from syphilis is greater than that of battle.

Troops upon the firing line with fresh or with contagious lesions of syphilis are usually removed to a hospital where they receive appropriate treatment, and are then returned; thanks to the more intensive ways in which arsphenamine is now administered this is usually possible in at least six weeks.

France has her battle lines divided into twenty-one divisions, with a base hospital for syphilis and gonorrhea for each division. This is usually considered the best method of treating syphilis

by those competent to understand the situation, and other nations are modeling their plans like the French.

Troops when upon furlough are apt either to acquire syphilis or to spread it, either to their own families or to women with whom they may have intercourse. How to control the spread of infection at this time is one of the most serious problems of the war, and one as yet unsolved.

When troops are discharged from the army the same thing is apt to happen as during furlough, and for this some provision must be made.

Not only the trooper and his immediate associates are to suffer from the ravages of syphilis, but society at large as well, as has already been pointed out in the first chapter of this book, and society must protect itself against not only the spreading of the infection to the innocent, but also against the economic losses incident to a spread of this disease. To do this no half-way measures can be taken, the firmest and most thorough are the best.

Various nations have made various attempts to prevent the spread of syphilis in the army. The French commission, composed of Belzar, Beclere, Bourquelot, Gaucher, Grunbert, Hallopeau, Landouzy, Pierre Marie, Pinard Pouchert and Vaillard recommended the following measures:

1. Medical supervision of all tolerated houses of prostitution consisting of daily visits, and bi-weekly visits to all registered prostitutes.

2. Sanitary visits by the military authorities every fifteen days.

3. Medical supervision of all inhabitants of a region occupied by soldiers, on their way to work.

4. Prohibition of street soliciting.

5. Police supervision of public houses.

6. Interdiction of women to the war zones, except those with permits.

7. Establishment of special hospitals for the treatment of venereal diseases for both military and civil cases.

8. Instruction of troops in reference to the dangers of venereal diseases.

In addition the French furnish a pamphlet to each of their soldiers, which reads as follows:[24]

Soldiers, Beware of Venereal Diseases

"(1) The venereal diseases, especially gonorrhea and syphilis, gravely affect the health. It is the duty of a good citizen and soldier to conserve his health for the service of his country.

"(2) Do not think that sexual continence is harmful. It conserves all the powers of the human body. It is quite apparent that it is the surest way of avoiding venereal disease.

"(3) Friend! have a care, for some day a veneral disease may be transmitted to your family, to your friends, and especially to your wife and children. Do not lose their love, esteem, and respect. Should you be honorable with your family? Would you have their love if you infected a sister or daughter?

"(4) Beware of all females who solicit the passerby in the streets. You may well know that they are infected and that you risk contagion through them.

"(5) Beware of their kisses, for the mouth of an infected person can give you syphilis, just as well as contact with their sexual organs. Do you know that venereal diseases are much more common now than in times of peace?

"(6) If at any time, in weakness, you have allowed yourself to be tempted by these women, do not forget to use a 'protector' of rubber. Also be careful to first oil your penis with some fatty substance, suet, oil or tallow, or, better still, with a disinfecting ointment containing 30 per cent of calomel. Do not touch either the mouth or sexual parts after sexual intercourse. Wash the penis and adjacent parts vigorously with soap and water, and if it is possible with a solution of bichloride one to a thousand. It is also best to urinate immediately after intercourse.

"(7) If you have a discharge you can be sure that you have a venereal disease, and go immediately to the doctor and continue with him until you are cured. He will be your sole confidant and counsellor.

"(8) It is also well to know that syphilis can be contracted in other ways than from a female, by contact with objects belonging to a person with syphilis such as cigarettes, pipes, glasses, forks, razors, napkins, handkerchiefs, etc. Beware of contact with persons whom you know have syphilis, men or women, as well as with objects which they may use.

"(9) A man affected with a venereal disease should abstain from all sexual intercourse. He should wash his hands after having touched his sexual organs. In case of syphilis one should kiss neither parents nor friends. The table utensils and his laundry articles should be used by him alone. Otherwise he risks giving the disease to others and adding to his troubles as well as prejudicing himself to society and his country. If a complaint be lodged against him, the judicial procedures will be severe.

"(10) In bewaring of prostitutes you guard your health for the girl whom you will marry and for the mother of your children. You may be sure that, thereby, during the war you will keep intact your courage and strength for your country."

Goodwin[25] considers that conditions in the English army are fairly satisfactory and he attributes them to the following factors: improved education of the troops, the provisions of games and recreations in the cantonments and the decrease in alcoholism. May[26] states that the use of female police has aided greatly in controlling women. The Royal Commission on Venereal Diseases[27] has recently issued an elaborate report, but one which to my mind is not sufficiently radical. It reports favorably on education, better diagnosis and treatment, the suppression of quackery and punishment for the willful communication of venereal diseases. As contrasted with the measures recently passed in Australia, and outlined elsewhere in this volume, it is decidedly weak. In Australia[28] it will be remembered that compulsory treatment by licensed practitioners is provided for.

The handling of the problem in Germany has recently been published in a special article in the *Journal of the American Medical Association*,[29] and I shall quote from this article. "The increased efforts for the control of the diseases have been extended not only to the part of the population which is in military service, but also to the civilians both in the military districts and elsewhere. The German efforts have taken two directions: first, the continental course of regulating prostitution and rendering it as little dangerous as possible, and, second, efforts to combat the venereal diseases directly.

"In military districts the most stringent regulation of prostitution has been effected, and outside of the military districts measures for the control of prostitution have been more rigorously enforced. Among German authorities, such as Neisser and Blaschko, there has been marked difference of opinion as to the sanitary value of regulation and examination of prostitutes. These measures are admitted by their advocates to be of only relatively small usefulness—certainly not of sufficient value to rekindle any hope of great benefit from them. German experts give the regulation of prostitution an entirely minor—if not, indeed, a negligible place—among the measures for fighting the venereal diseases.

"In Germany, as elsewhere, great stress is being placed on diagnosis and treatment for combating venereal diseases. The insurance companies, under which so large a proportion of Ger-

many's industrial population are being cared for, are furnishing general facilities for treatment of these diseases along the same lines that are being followed elsewhere. Government measures for providing universal opportunities are in process of establishment. * * * It is recognized that the weak point in this plan of treatment outside of the armies in Germany is the lack of authority to compel patients to continue treatment until they are freed from infectious danger to others.

"The recommendations for combating venereal diseases of a committee appointed to study this question by the Medical Association of Munich were recently reviewed in The Journal.[30] This committee presented a report which proposes to remedy the failure of patients to pursue treatment by requiring compulsory treatment as long as there is need for it. The recommendations of the Munich committee closely conform to the regulations which have been put in force in Western Australia. * * * Patients must seek treatment immediately on the appearance of the venereal disease. Suspects may be examined by boards of health and compelled to take treatment. Checks are provided so that patients who fail voluntarily to continue treatment will be compelled to do so, and, as in the Australian Act, heavy penalties are provided for the failure of patients or physicians to live up to their responsibility under the plan. The recommendations of the Munich committee go still further, and urge stringent measures for complete notification of the venereal diseases; but they recommend that the records of such notifications be provided with all possible safeguards of secrecy. The recommendations of this committee go much further than the general sentiment of the German profession. German medical authorities are agreed on the value of providing opportunities for treatment, and appreciate the need for measures to compel the continuance of treatment; but apparently there is wide difference of opinion as to the desirability and practicability of notification of the venereal diseases.

"The German efforts differ from others we have considered in placing important emphasis on the value as a sanitary measure of the personal prophylaxis of syphilis. Every effort is made to see that personal prophylaxis is carried out in the armies, and it is also being utilized among the civilian population. Where pre-

viously the condom was under legal ban as a means of preventing conception, its use to prevent venereal infection is widely and frankly advocated. Calomel ointment and other medicinal preparations for preventing infection are being distributed to soldiers and the public, and leaflets are being furnished which describe the methods of use of these devices. Neisser took the position before the Deutsche Gesellschaft für Bekämpfung der Geschlechtskrankheiten at its meeting in 1915 that measures of personal prophylaxis were of essential importance in the fight against the venereal diseases.

"Much anxiety is being shown in Germany concerning the danger of the spread of the venereal diseases by soldiers after their discharge, and vigorous methods are proposed for combating this danger. Neisser and others have urged that every soldier, officers included, should at the end of the war be given a Wassermann test, and an equally comprehensive plan is suggested for detecting gonorrhea among soldiers before their discharge. Blaschko's proposals, though less extreme represent the last degree of radicalism when compared with anything of this sort that has ever been done before. He proposes, before discharge, examination of the men who have suffered during enlistment from venereal diseases; retention under military control of men with active cases until a cure is effected; transference to the insurance companies for observation, and, if necessity should arise, for treatment, of men who have had venereal diseases during the war, but in whom the disease is no longer active. Many have urged the continuance of the severe restrictive measures which have been instituted and proved valuable under military rule, such as severe penalties for intercourse when persons are affected with venereal diseases, and the suppression of quackery. There is the same insistence on the continuance of the thorough military measures for diagnosis and treatment."

In the United States no systematic attempt has been made to decrease the amount of syphilis in either the army or the navy, and the result has been an appalling number of cases, the highest in any country. This is largely due to the fact that the services have not been taken out of politics and that various enthusiasts have been able to try beautiful moral schemes that

have not worked well in practice. Various enthusiastic and capable surgeons have done good work in limited fields, but as a whole the preventive work has not been good.

Cole is authority for the statement that when our regular army was on the Mexican border there were supervised prostitutes who lived with the army, being made a part of the regiment as it were. The prohibition of alcohol in the neighborhood of the camps and training stations is unquestionably of extreme value. Riggs[31] and Cole both report that the closing of the houses of prostitution has a beneficial effect.

The Surgeon-General's office has authorized a statement[32] on the social hygiene program of the War Department in relation to other agencies. So far the administrative measures may be grouped under five headings:

1. The army medical department will endeavor to instruct the men in the dangers of venereal disease, by talks, exhibits, pamphlets, etc. There will be prophylactic stations for lessening the danger of infection after exposure. Venereal diseases will be diagnosed early and effectively treated. Penalties will be imposed upon those men who persist in exposing themselves. Epidemiologic studies will be made.

2. The United States Public Health Service will promote public opinion in regard to social hygiene. It will survey and standardize hospital and clinical facilities for the treatment of venereal diseases. It will cooperate with private practitioners in lessening the dangers of dissemination. It will extend its laboratory, clinical and advisory service for venereal diseases in civil communities.

3. The civil authorities are to enforce the laws against prostitution and use of alcohol, establish suitable facilities for the proper treatment of venereal diseases, provide recreation for the population, educate and protect women and girls.

4. The commission on training camp activities is to enforce certain law measures, namely, elimination of commercial prostitution in the cantonment zones, repress clandestine prostitution, control sale of alcohol, combat the use of drugs and gambling. Also it is to provide recreation for the troops.

5. There are many useful opportunities for various nonofficial volunteer agencies. A small number of such agencies can be used as clearing houses for the work of all of them.

To sum up the means of prophylaxis and their relative values we may say the following:

1. Actively infectious cases of syphilis should not be admitted to training camps or other military duties until the lesions are sterilized: patients who have repeatedly suffered from mucous patches despite radical treatment should not be admitted at all.

2. Every possible means of recreation and amusement is to be encouraged: the relief societies have done good work that must be encouraged in every possible way.

3. The sale of all strong alcoholic beverages, and probably of beer and light wines as well, should be forbidden around cantonments and near the front. It is a well-recognized fact that many cases of syphilis are contracted while the man is under the influence of alcohol.

4. Street soliciting by women must be absolutely stopped.

5. Only women with permits should be admitted to all camps.

6. Inasmuch as we must look matters squarely in the face and recognize that a very considerable number of men will insist upon sexual indulgences available women should be carefully looked after. It is extremely questionable whether we should follow the example of some of the allies and have regularly licensed prostitutes, for this is bad morally and also, as Jolivet[33] has shown, far from safe, for supervised women can apparently disseminate venereal diseases just as readily as can clandestine prostitutes, and in addition the man feels that he is safe, and does not attempt to avoid infection. It would probably be well to have every soldier compelled to tell where he acquired his trouble and then put that woman under legal restraint, including treatment. In this work women police could be of great help. In addition any diseased woman who had intercourse should be liable to imprisonment, a fine would not suffice.

7. It is probable that those men who persist in sexual intercourse should be instructed in the use of condoms or urethral injections and mercurial ointments after intercourse. At the same time it should be remembered that Holcomb[34] has found that the latter means is not always efficacious. Yet other good observers feel that good results have been obtained by such means.

8. All troops should be educated in the dangers of venereal

disease, this can be done by personal talks, lectures, lantern slides, etc.

9. Troops should not be permanently removed from the firing lines because of syphilis, they should only be removed to receive treatment during the early stages, or when a late infection becomes active. To remove troops for venereal infections would be to encourage them to acquire such infections.

10. Treatment must be prompt and efficacious.

11. Any person who willfully transmits syphilis or gonorrhea should be subject to severe penalties.

12. Every soldier, officers included, should be thoroughly examined upon being mustered out of the service, or upon being sent home on a furlough, this should include a Wassermann examination. If diseased he should be required to continue treatment until cured.

13. In reference to syphilis among the civil population there should be national control, and not state control or no control at all, of the situation. It is only through one broad and strong policy that the necessary results can be accomplished. The West Australia laws could well be used as models.

Cole[35] well summarizes the methods of treatment that have been advocated in various countries. Although such an authority as Neisser[36] has recommended the ambulatory treatment of all cases of syphilis, still the weight of evidence is much against him, and it is now pretty well agreed that all early or infectious cases should be sent to a special hospital where they may secure appropriate treatment. As has already been pointed out France has her battle line divided into twenty-one divisions,[37] with a base hospital for venereal diseases located behind each. The personnel must consist of a head, and at least one assistant for syphilis and one for urological cases. Either the director or the syphilologist must be well versed in dermatology, because many skin diseases are so frequently mistaken for syphilis and vice versa. Pautrier has pointed this out very clearly. In addition there must be a dentist, as syphilitics who are to have intensive mercurial treatment need to have their mouths in the best possible condition. In each hospital there must be a laboratory where Wassermanns and dark-field examinations can be done. Personally I fail to see the need for animal experimentation in

connection with this war work, although many authorities consider it necessary. If possible there should be an x-ray outfit so that bone and aortic lesions could be early recognized. Certainly there should be a good general clinician attached so that visceral syphilis could be recognized. In regard to nervous syphilis it is probable that there should be one special hospital to which such cases should be sent: it is doubtful whether each of the venereal hospitals could find men competent to give intraspinous treatment.

In the hospitals it is essential to give the most rapid treatment possible. Our own army board consisting of Drs. Pusey, Pollitzer, Wende, Hagner and Morton[38] recommends that arsphenamine be given at five-day intervals. Personally I have been using arsphenamine at three-day intervals ever since hearing Pollitzer's paper.[39] Pollitzer it will be remembered recommended that three doses of arsphenamine be administered in three days, followed by a course of mercurial injections. I should strongly urge that five to six arsphenamines be given, at three-day intervals if the patients will tolerate them, otherwise as close together as possible. This can be followed by a course of mercurial injections, some of which could probably be given after the patient had been returned to the front.

In conclusion it may be well to point out the various recommendations which our Advisory Committee first made. First it points out the necessity of keeping complete case records, recommending the present army register for that purpose. Next it wisely points out the necessity of making an early diagnosis, especially insisting upon the use of dark-field illumination in all cases of venereal sores; in addition it recommends the obtaining of fluid from enlarged lymph nodes by aspiration in all doubtful cases. It also believes that the Wassermann should be done in all cases. Third it is not enthusiastic about the excision of the chancre, although recommending it in a half-hearted way; it appears to prefer a calomel ointment, which is in harmony with the generally accepted ideas. Fourth it believes in both arsphenamine and mercurial treatment, both strongly pushed. As regards the administration of arsphenamine it recommends that the first three doses be given at intervals of five days, and the remaining five at weekly intervals this to be combined with

either mercurial injections or inunctions. It also points out that such patients should be watched for a year with monthly Wassermann tests, and promptly treated should any evidences of a positive reaction become manifest. "In all cases seen after the Wassermann test has become positive the first course of treatment should be followed by a second after six or eight weeks' rest. And it is safest to give at least a third similar course after an interval of two months even in the most promising of cases." The discussion of the technic of administration requires no special comment as it is standard. In regard to mercury it states that a mercurial course should consist of six to eight weekly injections of an insoluble salt, or from thirty-five to forty-five inunctions. In late cases where there are no serious lesions it recommends mercury and potassium iodide until a symptomatic cure takes place. Unfortunately it does not recommend that such cases should receive sufficient treatment to render the Wassermann negative, a procedure which many of us believe to be imperative.

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CHAPTER XXIV

TREATMENT

Introduction

Necessity for Treating Syphilis.—A few years ago when Fournier[1] wrote his book upon the Treatment of Syphilis he deemed it necessary to first show that it was necessary to treat syphilis. Fortunately it is no longer necessary to produce any arguments to show that if this disease be untreated it is very apt to result most disastrously. All practitioners have seen many late cases that never had undergone the slightest medication. However, it may again be well to point out that every case should be treated, for although it is possible that the disease may occasionally spontaneously abort, yet this occurrence is extremely rare. Inasmuch as it is impossible to say just what the aftermath of any attack will be, each case should be treated vigorously.

Time for Beginning Treatment.—Every syphilographer, without exception now holds that treatment should be begun just as soon as the diagnosis is made. This applies especially to the chancre stage, where the outlook is much better if efficient medication is administered before generalization of the treponemata has taken place. We no longer wait for the appearance of the secondaries, for now by means of the dark-field illuminator we can diagnose syphilis positively just as soon as the initial lesion becomes manifest. Even in the late stages it is much better not to wait, for waiting may result in the destruction of tissue, but to administer treatment at once.

Excision of Chancre.—Only a few years ago there was great discussion as to whether or not syphilis could be aborted by the excision of the chancre as soon as it appeared. Even today Pollitzer recommends that this be done, accompanied, of course, by the administration of arsphenamine. However, the demonstration by Neisser[2] that the organisms can be found in the lymph

nodes, in the spleen, and in the bone marrow even before the chancre is manifest would seem to me to be good and sufficient reason against this procedure. It is probable that the local use of one of the mercurials is just as efficient.

Difference Between Treatment of Syphilis and of Syphilitic Lesions.—It is usually easy to clear up a syphilitic lesion, but this by no means indicates that the syphilis is cured, for to cure syphilis means that the treponemata must be eliminated from all of their hiding places, wherever they may be lodged, and this is a very different matter from clearing up a few superficial lesions. Fortunately the advent of the Wassermann reaction has impressed this fact upon the minds of the majority of physicians, although unfortunately not all patients as yet realize it.

GENERAL MEDICATION

Hygiene.—It goes without saying that a patient suffering from a contagious systemic disease, for such syphilis is, should live under proper hygienic surroundings, both for his own safety and for the safety of his associates. The latter point has been covered in the chapter devoted to Prophylaxis. The patient should lead a regular life, he should not overwork or overworry. Regular exercise in the open is most valuable, especially where there is any evidence of anemia. Under no circumstances should alcohol be permitted. In the first place the alcoholic is prone to overindulge when he remembers the disease that he has, and this is bad. In the second place there is a distinct impression on the part of many physicians that to some extent at least alcohol negatives the effect of mercury. If there be any throat lesions the use of tobacco must temporarily be interdicted. As regards diet there is but little to be said except that the food should be of good quality and mixed in character. Formerly it was considered by some authorities that green vegetables should not be eaten, but from a logical standpoint this seems absurd, especially when we consider how valuable such foods are in anemic conditions. Of course the food should be selected with an idea of keeping the bowels open, and plenty of water should be consumed. It is probable that the moderate drinking of tea and coffee has no injurious effects.

Tonic Treatment.—In many of the older books upon syphilis we find some such statement as the following: "No course of antisyphilitic medication is complete without the administration of iron: this is necessary for the anemia." In regard to such statements several answers may be made: in the first place in many persons it is impossible to demonstrate any noticeable amount of anemia, and in the second place it should always be remembered that good food and fresh air do more for anemia, after the specific cause is removed, than any amount of tonic treatment. At times, of course, it is necessary to give a bitter tonic for the whipping up of a jaded appetite, and in the case of a severe anemia iron may be used, but beyond this, tonic treatment need but rarely be employed.

Hydrotherapeutic Treatment.—For many years baths, especially baths from natural hot springs, have enjoyed a great reputation in the treatment of syphilis. The hot springs of Arkansas in the United States and Aix-la-Chapelle in Europe have been the mecca of syphilitics for years. Thompson[3] naturally has more to say on this subject than any of the other authors of text books upon syphilis. He states: "The benefits to the syphilitic derived from a sojourn to the Hot Springs have variously been ascribed to a specific action of the waters, both as baths and taken internally, to the greater elimination produced, to stimulation, to the routine life, and to the effects of the salubrious climate. The alleged specific effect of the waters has been said to be due to some peculiar chemical combination of the solids in solution, to electricity produced by chemical decomposition, to a peculiar heat with which they are imbued, and latterly to the radioactivity which they have been shown to possess."

As regards these points Keyes[4] states: "My observation showed me that the patients who did well at the springs used most unsparingly mercury by inunction and iodide of potassium internally in enormous doses. And this is exactly where the value of the springs seems to lie. Patients broken down, cachectic, with faulty stomachs, who have syphilitic lesions which fail to yield at home because they can not tolerate a sufficiently high degree of medication, these are the patients to send to the hot springs. There, under the assistance of the hot water internally and the

baths, they can take a mercurial friction day after day, without salivation, which would overwhelm them at home, and their doses of iodide of potassium can be quadrupled without upsetting the stomach. I have verified this over and over again. This is the only class of patients I ever send to the springs—those requiring stiff medication for serious lesions which can not at home be made to tolerate a sufficiently high dose to pull them through."

White[1] states concerning the types of patients who should be sent:

"1. The patients whose mode of life is objectionable and who can not be controlled while under home or other customary influences. This includes not only the large class of hard drinkers, who are apt to use tobacco too freely and to indulge in various other excesses, but also the much smaller class whose excessive devotion to work or business interferes with their general health and lessens their strength and vitality.

"2. Patients whose symptoms resist full doses of the specific drugs and who are unable to take larger doses without a breakdown of the digestive apparatus, or the production of mercurial or iodic intoxication. Those especially should be sent who have involvement of the viscera and still more particularly if the brain or spinal cord be affected.

"3. Patients who have syphilis with intense syphilophobia and require the mental impression, and in addition the tonic influence of change of scene and climate.

"4. Patients with defective elimination or with marked idiosyncrasy as regards either mercury or the iodides."

Thompson confirms these views, and believes that the chief benefit is from the ability to take more antisyphilitic medication than under ordinary circumstances. Thompson gives the following as a general outline of the treatment given:

"The patient is placed in a tub of hot water at a temperature of 35.5° C. to 38° C. (96° F. to 100° F.) where he remains from eight to fifteen minutes. When free diaphoresis is desired he is placed in a hot wet pack and covered with blankets for fifteen to thirty minutes, and when more profuse sweating is wanted the vapor cabinet is used for three to five minutes. Usually in the tub and in the pack the hot water is taken to

drink to assist in promoting diaphoresis. Generally following the pack a shower and needle is given for two to three minutes beginning at a temperature of 38° C. (100° F.) and being reduced to 32° C. or 27° C. (90° F. or 80° F.). Following this the patient sits or lies in the cooling room until cool and the skin is dry. Ordinarily the patient spends from one and a half to two and a half hours at the bath house."

Personally I am inclined to believe that the chief benefit that has come from visits to the springs comes from the fact that the patient is better under the control of the physician, and that possibly an ability to take more mercury is a secondary matter. In the new days of arsphenamine it usually makes but little difference whether or not the syphilitic can ingest mercury freely.

General Precautions.—In all cases of syphilis it is of the utmost importance that the teeth be kept clean. From time to time various tooth washes have been recommended, but the really essential thing is to keep the teeth clean and to cure any pyorrhea that may be present. A thoroughly competent dentist is a great asset to the syphilologist and also to the patient. Another very important point that is too often overlooked is the weekly examination of urine, especially for albumin. Either syphilis or mercury may cause kidney irritation, and every patient who is taking mercury is improperly handled unless his urine be repeatedly examined.

SPECIFIC MEDICATION

To control or cure syphilis we have at our disposal three chief drugs: mercury, the iodides, and the arsenic derivatives. From time to time other drugs have been recommended, but none have stood the test of time in the way that these three have.

Mercury

According to Buret[6] the Chinese used mercury as far back as 2637 B.C. in the treatment of syphilis. While this statement may be disputed on good grounds, yet it is true that mercury has been used almost as long as the disease has been known. In 1530 Fracastor[7] wrote:

"As a fact, the action of mercury on the scourge is marvelous,

either because its natural affinity for heat and cold renders it proper to absorb the devouring fire of the disease: or, because its surprising density permits it to divide and to dissolve the humors for a reason that is analogous to that which gives to incandescent iron a caustic action more marked than that of a light flame: or that its mobile and penetrating molecules, apt to infiltrate themselves in the warp of tissues, have the power of pursuing and consuming the impure yeasts of the disease; or finally that its magic virtues are derived from some occult force whose mystery escapes us."

In spite of arsphenamine, mercury is still used, and seems destined to be used as long as we have syphilis with us.

Pharmacologic Action of Mercury.—Nichols[8] as the result of much careful experimental work has the following to say in regard to the action of mercury upon the treponemata: "I have worked chiefly with single intravenous injections of the bichloride and salicylate of mercury in order, if possible, to obtain a better comparison with salvarsan. I have found under these conditions that no action can be demonstrated for mercury much short of the fatal dose. The tolerated dose for mercuric chloride is 0.001 gram per kilo, but no definite spirillicidal action is present with this dose; if, however, the dose is raised to 0.003 grams the spirochetæ are destroyed in forty-eight hours, but the animal eventually dies of nephritis.

"The same is true of the salicylate. The tolerated dose of 0.005 gram per kilo has no curative effect, but a dose of 0.0075 or of 0.01 gram will destroy the parasites promptly, although the animal usually later dies of nephritis. In these experiments the insoluble form of mercury salicylate was mixed with equal parts of potassium carbonate to dissolve it. Rabbits are, of course, subject to nephritis naturally, but the lesions found after injection of mercury were so definite and the mortality was so great that no doubt was left as to the cause of the condition. * * *

"It is evident from these results, as well as those of other observers, that mercury has some selective action for spirochetæ; but it is evident that the margin between the parasitotrophic action and the organotrophic action is not nearly so great as it is with salvarsan, from which one can understand why it is necessary to continue mercury so long clinically to get

beneficial results. It is also evident that the intensive treatment with mercury is indicated in order to kill the spirochetæ promptly, and that at the same time the effects on the kidneys must be watched constantly."

Toxicology of Mercury.—Schamberg, Kolmer and Raiziss[9] have recently published a complete article upon the toxicity of mercury. As regards the immediately fatal dose per kilo of body weight they present the following table, which is also valuable as showing the amount of mercury contained in the various salts.

	IMMEDIATE LETHAL DOSE	CONTAINED MERCURY	AMOUNT PURE MERCURY
1. Hg salicylate	0.027 gm.	58%	.0155
2. Hg sozoiodolate	0.024 "	32%	.0077
3. Hg cacodylate	0.37 "	20%	.0075
4. Hg benzoate	0.015 "	45%	.0067
5. Hg bichloride	0.007 "	74%	.0052
6. Hg oxycyanide	0.0055 "	83%	.0045
7. Hg succinimide	0.007 "	50%	.0035

The authors reach the following conclusions:

"1. Rats exhibit such variation in their resisting power to mercury that too much weight should not be attached to minor differences in toxicity in the experimental findings.

"2. While the maximum tolerated dose of the various salts may be widely divergent, when the doses are calculated in terms of pure mercury, they fall within relatively narrow limits.

"3. In general terms it may be stated that the toxicity of the mercurial salts is directly proportionate to the amount of mercury contained.

"4. The inorganic salts, as represented by the bichloride of mercury, are no more toxic than the numerous organic combinations that are commonly employed.

"5. The differences in the molecular structure of the mercury compounds tested by us were found to be of relatively little importance as affecting their toxicity.

"6. The bichloride of mercury was fatal, on the average, in intravenous doses about 2 milligrams per kilo of body weight; administered intramuscularly it was fatal on the average, about 6 mg. per kilo of body weight.

"7. The average relationship as to the toxicity between the intravenous and intramuscular administration of mercury, in general, was about 4 to 1.

"12. Mercury has a great affinity for the cells of the kidney, and this organ is one of the first involved in mercurial intoxication. Hence during the intensive treatment with mercury, the necessity of careful examination of the urine from time to time should be emphasized. * * *

"13. The nephritis produced by mercury is primarily tubular in character; capsular glomerulo-nephritis of the exudative (hemorrhagic) variety is frequent and practically always accompanies severe tubular nephritis. Calcification of the degenerated tubular cells has been found within forty-eight hours after the administration of mercury and always occurs in severe mercury nephritis, irrespective of the salt administered or the route of injection."

Fate of Mercury in the Body.—According to the *Manual of Venereal Diseases*[10] mercury can be detected in the urine two to three hours after it is injected, twenty-four hours after it has been rubbed in, and three days after it has been ingested. However, mercury lingers in the body a long time. Lang[11] states that it could be found in the system two years after inunction in two patients. It reaches all organs of the body. It is eliminated by the saliva, sweat, bile, milk, urine and feces.

Contraindications to the Administration of Mercury.—Mercury should be used with great care in the acute infectious diseases, in those who have recently recovered from dysentery, severe diarrhea, and malaria fever.[12] In addition tuberculous patients often do very badly under mercury. Persons suffering from nephritis, except syphilitic nephritis, must take mercury with great care, inasmuch as it has such a great action upon the kidneys. Fortunately salvarsan is much better borne in these cases. If patients lose much weight mercury should be discontinued. Patients suffering from malignant syphilis usually tolerate mercury very badly, and the initial dose in such cases must be small. Severe diarrhea or the presence of other manifestations due to mercury are indications for temporarily stopping the drug.

Untoward Effects of Mercury.—The chief evil effects of mercury are salivation, nephritis, gastrointestinal disturbances, cutaneous eruptions and loss of weight; more rarely bronchitis may result.

Salivation.—Salivation is no longer common, although formerly it was regarded as being almost necessary. A strange opinion that is still held by some physicians is that mercury will never salivate a syphilitic patient: this is certainly not true. In the old days salivation meant marked inflammation of the gums and mucous membranes of the mouth, a profuse flow of saliva, and often necrosis of the jaw with loss of teeth. At the present time if we note any inflammation of the gums we promptly stop the administration of the drug. As already mentioned in this chapter salivation can often be prevented by absolute cleanliness of the teeth and mouth.

The first symptom of salivation is usually a metallic taste in the mouth. Almost immediately it is noted that there is some sensitiveness when the teeth are "clicked together." About the same time a little swelling of the gums behind the third lower molars, and less frequently back of the lower incisors, may be seen. In some instances it is surprising how rapidly such symptoms may develop even in a clean mouth: I have seen a patient develop mercurial stomatitis after six days' treatment with protiodide pills, only three-fourth grains a day. At other times a patient will stand three times that dose over long intervals without any trouble whatever.

The treatment of mild cases of salivation consists in the withdrawal of the drug, and touching the gums with an antiseptic solution, such as a 50 per cent solution of tincture of iodine, and washing the mouth several times a day with potassium chlorate solution. In cases of severe stomatitis the patient should be put at rest, preferably in a hospital and given a liquid diet. Saline laxatives and diuretics, as well as plenty of water, should be administered. Hot packs may be very useful. The mouth must be thoroughly cleansed every few hours.

The diagnosis of salivation has been discussed in the chapter upon Affections of the Mouth.

Nephritis.—As already indicated, mercury can cause a tubular nephritis. I have seen this result from three days' treatment

with protiodide pills, yet, on the other hand, large quantities of mercury may be taken for a long time without one being able to find any abnormalities in the urine. As a rule the presence of albumin, together with blood and granular casts is one of the first evidences of kidney irritation, then the output of urine becomes markedly diminished, and blood may appear. The specific gravity is always high. Mercurial nephritis may completely resolve, or it may result in a chronic nephritis; all depends upon how much damage has been done to the secreting epithelium. The diagnosis must be made from syphilitic nephritis, and this point is discussed by Dr. Fowler in his chapter upon Syphilis of the Male Genitourinary Tract. As a rule syphilitic nephritis is relieved by antisyphilitic medication, while mercurial nephritis is made worse. The immediate prognosis of the mild cases is good, and even many of the severe cases recover. Mercurial nephritis can usually be prevented by carefully watching the kidneys during the early administration of mercury, during the first weeks of mercury the urine should be examined at least twice a week as a routine. The treatment of mercurial nephritis is that of acute nephritis in general. The offending substance must be withdrawn, the patient kept at rest and with a bland, nonirritating diet, preferably one of milk. The bowels must be kept thoroughly open, and copious sweating should be induced. For reference the writings of Wells,[13] Pollock,[14] Pearce,[15] Klienberger,[16] Ophuls,[17] Stein[18] and Hazen[19] may be consulted.

Gastrointestinal Disturbances.—Every physician realizes that mercury is prone to upset the digestive tract, usually causing diarrhea with griping, but often various gastric symptoms as well. In such cases it is usual to diminish the dose of mercury somewhat, and to give either paregoric or Dover's powders with the mercury. At times the mercury with chalk seems to be better borne than any of the other preparations.

Cutaneous Eruptions.—According to the majority of English and American writers it is rare to find cutaneous eruptions as the result of mercury administered for syphilis, and this is probably true for the author has seen but one case. Mercury, of course, may cause eruptions in either one of two ways, first by its local action when rubbed into the skin, and second by its excretion through the skin after being absorbed from any

portal of entry. Here we are concerned only with the second class. Fournier[20] states that the eruption usually appears rather soon after the administration of the drug, and that it is unusual for other signs of mercurial poisoning to accompany it. The following types of eruption may appear: most commonly a generalized desquamative eruption that is prone to itch intensely, and an urticarial or erythematous rash that is limited to circumscribed regions, such as the groins and axillæ. Such eruptions are prone to recur each time that mercury is administered.

Loss of Weight and Strength.—A rather high percentage of syphilitics can not take mercury in large doses for any length of time without losing considerable weight and often feeling depressed and languid. Such persons should discontinue the drug until the weight is restored to normal, unless there be urgent reasons for pushing the medication. Usually it is wise to substitute arsphenamine in these cases.

Clinical Results from Mercury.—There can be no doubt that mercury usually causes the lesions of syphilis to disappear; this at times is true even of cerebrospinal lues. On the other hand, the use of the Wassermann reaction has shown us that the vast majority of these cases are not cured, and that the treponema is simply kept chained as it were. Nichols' work, already quoted in this chapter, shows that mercury can not be used in sufficient dose to kill the organisms unless the patient also be most severely damaged. On the other hand the figures quoted by Fournier and Neisser (see chapter on Prognosis) show beyond any matter of dispute that those patients who have regularly taken mercury do not begin to suffer from the late accidents of syphilis so frequently as those who have taken insufficient treatment. It is still questionable whether or not mercury has ever cured syphilis. Judging from the experimental work on the subject it has not, and yet every syphilologist has seen numerous cases that have had much mercurial treatment, and which have remained clinically and serologically well for more than two years; this question must still be viewed with an open mind, although there can be no doubt but that in an overwhelming majority of instances syphilis is not cured by mercury.

Serologic Results from Mercury.—There is a large amount of literature dealing with this important point, and only the most important articles can be quoted. Fox[21] has collected the following statistics:

NAME	NUMBER OF CASES	METHOD OF TREATMENT	% NEGATIVES
Müller	48		37.5
Lederman	92	One to three courses	26.
	59	Four or more courses	52.
Bering	69	Well treated by chronic intermittent	84.
Citron	58		46.5
Fischer	62		48.
Blumenthal	95	One to five "Kuren"	51.
Lesser	115	Well treated by "Kuren"	62.
Blaschko	90		84.
Mauriac	33	Well treated	60.
Pürckhauer	116	One or more "Kuren"	65.
	54	One to four "Kuren"	68.5
Höhne	127	Well treated by injections and inunct.	52.
Jesionek	216	One to three "Kuren"	45.
	130	Four to eight "Kuren"	61.
Bruck			70.
Harrison	49	Two courses injections or inunct.	22.
	69	Six to eight courses	59.
Seligman	166	One to three "Kuren"	25.
	38	Four to ten "Kuren"	55.
Feuerstein	112		42.8
Almkvist	102		70.
Boas	231	Well treated	79.
Gavini	139	Little treatment	23.
		Energetic treatment	85.
Marcus	200	Ten "Kuren" by injections	87.
Gennerich	124	Injections and inunctions	75.

According to Noguchi,[22] Lesser states that a positive reaction can be made negative in about 35 per cent of cases by giving 30 inunctions of mercury, 12 injections of an insoluble mercuric preparation, or 25 injections of a soluble mercuric preparation. Matson and Reasoner[23] found that in cases of less than one year's duration the Wassermann became negative in the vast majority on two months' treatment with injections of the red iodide of mercury. They also found that the effect of mercury by mouth

was much less. However, they reported that many of the cases relapsed to a positive in a short space of time. In contrast with all of the above figures the work of Nelson and Anderson[24] and of Craig[25] must be mentioned. The former report fifty cases all of which remained positive at the cessation of the treatment with injections of the salicylate. Craig gives the following figures:

METHOD OF TREATMENT	TIME OF TREATMENT	NUMBER OF CASES	CHARACTER OF REACTION ++	+	+−
Internal	9 months	17	8	7	2
Internal	12 months	26	16	8	2
Internal	2 years	17	7	9	1
Internal	3 years	8	3	4	1

Certain deductions can at once be made. Injections or inunctions give a negative reaction much sooner than does medication by mouth, while inunctions are about as good as injections. In view of the difficulty in telling just what treatment was administered in many instances absolute deductions are not justifiable.

Method of Administration.—Mercury is administered to syphilitic patients in several different ways, the most popular being by mouth, by inunction and by injection. Less used methods are by fumigation, inhalation, and by suppositories.

Administration by Mouth.—Various preparations of mercury have been employed by mouth: the following are the chief ones: protiodide, salicylate, gray powder, bichloride, calomel, blue mass, tannate, carbolate, peptonate, acetate, sozoiodolate. In America the most popular preparations have been the protiodide and the bichloride, the latter usually being combined with potassium iodide. Unquestionably the protiodide pills are just as effective as any other form of mouth medication. The dose with which the patient is usually started is one-fourth of a grain three times a day after meals, and this may be doubled if the patient stands the drug well. Fournier[26] considers that the protiodide is more apt to cause salivation than are some of the other salts, but that it effects the digestive tract less. It is worthy of note that Ricord first popularized the use of the protiodide, and the formula for his pills was:

Protiodide of mercury	1 gm.
Extract of opium	1 "
French lactucarium	3 "
Confection of roses	6 "

Divide into sixty pills.

For all practical purposes the ordinary protiodide pill is as satisfactory an internal remedy as we have at our disposal.

Salicylate of mercury may be given in $\frac{1}{5}$ grain doses three times a day, and this may be slightly increased. It has no advantage over the protiodide. It was introduced by Silva Araujo,[27] of Rio Janeiro.

The gray powder, or mercury with chalk, is very popular with the English syphilologist. Jonathan Hutchinson[28] repeatedly advocates it. It is usually administered in either pill or capsule form. It contains 38 per cent of mercury and the dose runs from two to eight grains.

The bichloride is extensively used with potassium iodide, this being known as mixed treatment. Occasionally it is employed alone, the dose being not over $\frac{1}{16}$ of a grain three times a day. Osler was fond of it in smaller doses. There are a large number of preparations that have been employed. Some of them are:

1. Van Swieten's liquor,

Distilled water	900 grams.
Alcohol, 90 per cent	100 "
Bichloride of mercury	1 "

This is given in tablespoonful doses after meals.

2. Dupuytren's pills, which now have the following formula:

Bichloride of mercury	1 centigram
Extract of opium	2 centigrams
Extract of guaiacum	4 "

Fournier states that the old formula which contained but one sixth as much opium is the preferable one.

3. Mixed treatment.

Bichloride of mercury	0.1 gm.
Potassium iodide	15.0 "
Aquae q.s. ad	90.0 c.c.

This is given in teaspoonful doses after meals, well diluted with water. This remedy is also put up in pills by various com-

mercial houses. By many sarsaparilla is added for its flavoring properties.

Calomel is but little used, because if given in small doses it is very prone to salivate, and if given in large doses it is not absorbed.

Blue mass (massa hydrargyri) has been extensively used, but inasmuch as it readily salivates it is no longer much employed. The dose is one grain.

Mercury tannate has been widely recommended, but it apparently has no advantages over the other preparations.

The various other preparations are fully discussed by Lambkin[29] and by Fournier.

Although it has been shown time and again that the giving of mercury by mouth does not affect the Wassermann reaction so promptly as when administered by injection or inunction, it will doubtless always continue to be popular, simply because it is the most convenient way for the patient, there being no pain, no dirt, and no occasion for frequent visits to the doctor. On the other hand there are several disadvantages outside of the great one that it is not so efficient; it is impossible to tell whether or not the patient is taking the drug regularly and he may escape from observation and merely drug himself.

Administration by Inunction.—Fournier gives an interesting historical survey of this method, stating that "this is the oldest of all methods of the administration of mercury." In the early days it was administered most recklessly, and the patients soon suffered more from the treatment than from the disease, for it was believed that salivation meant that the poison of syphilis was being excreted through the saliva! "Such was the treatment of syphilis by inunction even in the first third of the nineteenth century." At the present time there is considerable discussion as to just how the mercury is absorbed when rubbed in. It was formerly believed to be by absorption, but Welander's work threw doubt upon this, and rather tended to make one believe that it was by inhalation of the volatilized mercury. Very recently the question has again been investigated by Wile and Elliott,[30] who believe that it is absorbed both through the skin

and lungs. Their experimental work seems to indicate that calomel is more readily taken into the system than the ordinary mercurial ointment.

The preparation usually employed is the strong mercurial ointment, but the official oleate ointment also has some advocates, chiefly because it is comparatively clean. The average dosage of either preparation is about one dram, and this may be increased to one and one-half drams when it is well borne. It is essential that the proper amount be used, and this should be weighed or measured in an accurate way. A different part of the body should be selected for each of seven nights, and always a part that is hair-free for if mercury be rubbed in around hairs a pustular dermatitis is apt to result. We usually give the following directions to the patient. The first night rub the ointment into the inside of the right arm, the second night into the left arm, the third night into the inside of the right leg, the fourth night into the left leg, the fifth night into the right flank, the sixth night into the left flank, and the seventh night into the abdomen. On the eighth night begin again with the right arm. The part to be used should first be washed with hot water and soap, and the ointment should be well rubbed in, this may be done either by the patient himself or by some one else, and in the latter case the back becomes available. The rubbing should be continued until the ointment has disappeared, which usually takes about twenty-five minutes.

This method has the advantage of being very effective if properly carried out, but we have practically discarded its use in dispensary work for the good and sufficient reason that patients will not carry it out properly. On the other hand, in hospital wards it is frequently employed, and with excellent results. Experimental work has shown that this method is almost as effective as the injection method. It has the great disadvantage of being very dirty, so that the patient can not conceal what he is doing, and also it takes a considerable amount of time.

Recently Schamberg and his coworkers have suggested that calomel inunctions might be substituted for metallic mercury ointments. The formula that they suggest is:

Lanolin	1 gm.
Benzoinated lard	2 "
Calomel	3 "

(Schamberg, Kolmer, Raiziss and Gavron: Jour. Am. Med. Assn., Jan. 19, 1918.)

Administration by Injection.—It is probable that Hebra[31] in 1861 was the first to employ the method of hypodermic injection in the treatment of syphilis. He was followed by Scarenzio[32] in 1864, and Hill[33] in 1866, but Lewin[34] in 1869 was the first to attract serious attention to this method. At first injections were made simply into the subcutaneous tissues and abscess formation was not infrequent, but since Balzer[35] in 1888 pointed out that the injections should be made deep into the muscles there has been but little trouble on this point.

The technic is simple, the patient should bare his gluteal muscles and lie upon his abdomen. The text books and articles give elaborate directions as to just the site that should be chosen for injection, but to me this seems folly, inasmuch as it is rarely possible to make two injections in the same place, at least for several months. However, the upper and outer quadrant of the gluteal muscles should always be chosen, so as to keep away from the nerves and vessels. The skin may be cleansed with a 50 per cent solution of iodine, or simply with alcohol. An all-glass syringe, preferably a 2 c.c. Luer type, is employed; the needle should be 18 gauge, and at least one and one-half inches in length, and should always be sharp. For the insoluble salts a steel needle may be used, but for the soluble salts a platinoiridium one is preferable, as it will not corrode, although a steel one may be used if it is thoroughly washed immediately after injection. The patient then contracts his gluteal muscles, and the needle is plunged at right angles into the muscles, this being done in one motion. It is really surprising how little pain is occasioned by such an injection if the needle is sharp. Then the plunger should be drawn up slightly to make sure that the needle is not in a blood vessel. Then the injection is slowly made, and a little air should be injected following the mercury suspension or solution. This is to plug the hole and keep any of the mercury from flowing back into the subcutaneous tissue. The needle is then rapidly withdrawn and the finger at once put over the hole and deep pres-

sure made, together with a rotary motion that acts as massage. If this be properly done it is very rare for any of the solution to escape; if any of this be seen flowing out the physician can be almost sure that the patient will have an abscess or at least an area of inflammation.

There are two classes of mercurials used for injection, the soluble and the insoluble. The soluble preparations include the bichloride, the succinimide, the benzoate and the cyanide, while the most important of the insoluble preparations are calomel, gray oil, the salicylate, the protiodide and the tannate. The soluble preparations are supposed to be absorbed very promptly into the bodily economy and to have a rapid effect, whereas the insoluble preparations form a nucleus of mercury in the tissues from which absorption takes place slowly; hence if one wants an immediate effect the soluble salts should be chosen, while for routine treatment the insoluble salts are preferable. Schamberg, Kolmer, and Raiziss[36] have shown that something over 1 per cent of the salicylate, gray oil and calomel are absorbed each day. As regards the vehicles used for the insoluble preparations there has been much discussion. Paraffin oil is one of the most popular, but there is a theoretic objection, as pointed out by Sutton,[37] that an insoluble paraffinoma may result. Personally I consider that this is overrated, but nevertheless the possibility should always be remembered. Aja[38] believes that the best vehicle is solid vaseline, with liquid petroleum occupying the second place. He thinks that lanoline causes pain, and that both castor oil and olive oil are painful and not well absorbed. Cocoa butter seems to work very well, and Lambkin has suggested palmitin, but inasmuch as this substance is extremely expensive its use seems out of the question as a routine vehicle.

Calomel is considered by Fournier and Lambkin[39] to be the most efficient of the mercurial injections, but I quite agree with both writers that it is usually extremely painful. To overcome this Lambkin has proposed the following formula:

Calomel	5 gm.
Guaiacol	10 "
Camphoric acid	10 "
Palmitin q.s. ad	100 "

Ten minims of this preparation contains one-half grain of calomel. Lambkin states that the injections of this preparation are almost painless, but nevertheless he does not advocate them for a routine treatment, although he does state that it is the most efficient antisyphilitic mercurial preparation that we have. After considerable experience with Lambkin's formula I do not wonder that he does not employ it to the exclusion of other remedies, for it certainly is far from painless, and despite the utmost care in using it I have had abscesses in not far from 10 per cent of my cases. Since the introduction of salvarsan I have not employed it in a single instance. However for those who wish to use it I should recommend the following formula:

Calomel	5 gm.
Guaiacol	10 "
Camphor	10 "
Liquid petrolatum	100 c.c.

Use about fifteen minims once a week.

Pellier[40] has written an excellent article as to the absorption time of calomel from the tissues of man. I have already called attention to the reports of Schamberg, Kolmer, and Raiziss on the same subject.

Metallic Mercury.—Metallic mercury is preferred as the routine intramuscular salt by many excellent syphilologists, including the men of the English Army, Reasoner of the American Army, and Fordyce of New York. The gray oil, or oleum cinerum, was originally introduced by Lang in 1884. His formula has been modified several times, and according to Lambkin the latest is:

Metallic mercury	2 parts.
Sterilized anhydrous lanolin	1 "
Sterilized liquid paraffin	1 "

Lafay's well-known formula is:

Metallic mercury	40 parts.
Sterilized anhydrous lanolin	12 "
Sterilized white vaseline	13 "
Sterilized oil of vaseline	35 "

Lambkin recommends practically the same formula as for calomel:

Metallic mercury	10 parts
Guaiacol	10 "
Camphoric acid	10 "
Palmitin q.s.	100 "

Personally I am using the formula suggested by Fordyce, with excellent results. This is:

Redistilled mercury	30 parts
Lanoline	45 "
Olive oil	75 "
Chloretone	15 "

The Lambkin formulas have always proved troublesome, for abscesses were only too common, despite the greatest care.

Salicylate of Mercury.—This preparation is preferred by many men, and is unquestionably the salt most frequently used in America. Clinically the results are frequently excellent, although the late work of Noble and Anderson[41] has thrown some doubt on its effect on the Wassermann. At this point it may be stated that many excellent syphilologists do not coincide with the views of these two observers. Many different types of vehicle have been recommended. Personally I use the following:

Salicylate of mercury	2.5 gm.
Guaiacol	2.0 "
Camphor	2.0 "
Liquid petrolatum q.s. ad	30. c.c.

The guaiacol and gum camphor do two things: they diminish pain and they keep the preparation sterile. For clinic work this second point is important, for large quantities of the preparation can be made up at one time. For private work either the same preparation can be used, or the ampules put up by various manufacturers may be adopted: some of these are excellent. Urea and quinine hydrochloride or chloretone may be added as analgesics. Men almost without exception stand the salicylate without any local trouble, but some women can not take it without pain.

Biniodide of Mercury.—This salt is sometimes grouped under the soluble salts, but as a matter of fact it is probably converted into the albuminate of mercury as soon as it enters the tissues, hence is really an insoluble preparation. It is agreed by almost

all observers that the biniodide is less efficient than the three salts already described, and yet it is so much more efficient than mercury by mouth and gives so much less trouble when injected than any of the other insoluble preparations that it will doubtless continue to be used for many years to come. It may be dissolved in oil according to the following formula:

Mercury biniodide	0.015 gm.
Castor oil	1. c.c.

Or olive oil may be substituted for the castor oil.

Or it may be dissolved by the addition of sodium or potassium iodide:

Mercury biniodide	0.015 gm.
Sodium iodide	0.015 "
Distilled water	1. c.c.

The second formula is unquestionably superior to the first in that it gives much less pain and induration. Almost anyone can stand it, no matter how sensitive he may be to the other mercurials.

Treatment by the Insoluble Preparations.—As a rule a course of treatment by the injection of insoluble mercurial salts means from twelve to twenty injections administered at weekly intervals. Usually patients will take no more without the danger of nodosities in the buttocks. To offset this it is possible to utilize the lumbar muscles, and these seem to stand a few injections remarkably well.

Disadvantages of the Insoluble Mercurials.—There are several undoubted disadvantages of the form of treatment by weekly injections of the insoluble preparations. The question of immediate pain is usually so slight that it can be disregarded, but there is nearly always some soreness that lasts for a day or two, and this may be very severe in the case of certain of the preparations. After any of the salts have been administered over a considerable space of time nodosities, often painful, usually result, so that the injections must be discontinued. Abscess formation is not common if a careful technic is employed. One real disadvantage is that if mercurialism develops it is impossible to

remove the source from which it is being absorbed, and yet if no further injections be administered it is usual for such symptoms to disappear quite promptly. Much has been written of pulmonary embolism following such injections, and a large number of cases have been reported: however such accidents are almost always the result of faulty technic. Lassere[42] has collected the reports of about fifty deaths after treatment by the insoluble injections, usually due to embolism and Mallein[43] has reported a number of other cases. Hence it is evident that such treatment must not be used carelessly.

Treatment by Soluble Mercurial Salts.—The bichloride of mercury is much used by many men. Personally I do not like it, because it gives much pain in many instances. It is usually given in doses of from $\frac{1}{12}$ to $\frac{1}{2}$ a grain either daily or every second day. The following prescription is the one in common use:

Bichloride of mercury	2 gm.
Sodium chloride	1 "
Distilled water q.s ad	100 c.c.

The succinimide of mercury is the salt that I have usually employed. It comes in one-fifth of a grain hypodermic tablets, and hence is very convenient. Under no circumstances should it ever be administered subcutaneously, as severe inflammatory reactions may result. It is possible that kidney irritation may readily be induced by this salt, but not probable that it is any more irritating than any of the other soluble salts. As a matter of fact Schamberg's experiments apparently showed that it was the best tolerated of the soluble salts. Another formula that may be employed is the one suggested by Thompson:

Mercury succinimide	2.5 gm.
Beta-eucaine	0.5 "
Water q.s. ad	100. c.c.

The average dose is about two-fifths of a grain three times a week. When given deep into the muscles there is very little reaction from this remedy.

The benzoate of mercury was first suggested by Stukobenkoff,[44] and has since been used rather extensively. One-sixth of a grain

is given at a dose. Thompson speaks highly of it and recommends the following formula:

Mercury benzoate	2.0 gm.
Sodium chloride	2.5 "
Water q.s. ad	100. c.c.

The cyanide is likewise recommended by some men, after having been introduced by Cullingworth.[45] The dose is about the same as for the other salts.

Other articles that deal with the intramuscular injection method of treating syphilis are those of Welander,[46] Pernet,[47] Pellier,[48] Shields,[49] Gottheil,[50] and Candler.[51]

Intravenous Injections of Mercury.—Mercury was first used intravenously by Bacelli[52] in 1893. Others who have used it are Pernet,[53] Bernart,[54] Crume,[55] Lydston,[56] Kingsbury and Bechet,[57] Stukes,[58] Lane, Barthelmy and Levy-Bing[59] and others. However it has never come into general use, and is not highly recommended by those who have given it a trial. The chief objection seems to be the phlebitis that is so apt to result, even in dilute solutions. Unquestionably this is the quickest way of getting mercury into the system, but now that arsphenamine is available this method seems useless. The salt that has been most used is the bichloride in doses of from $\frac{1}{12}$ to $\frac{1}{2}$ grain. The cyanide, biniodide and benzoate have also been recommended. The usual method has been to dissolve the mercury in from 5 to 15 c.c. of distilled water, or in normal salt solution, and to inject with a syringe into one of the arm veins. Thompson[60] states that he has been completely able to overcome phlebitis by the following procedure: "From 40 to 50 c.c. of blood are collected by venipuncture and placed in a large test tube which has been autoclaved. After separation the serum is poured off and thoroughly centrifugalized. A watery solution of mercuric chloride is prepared so that each cubic centimeter contains 22 mg. ($\frac{1}{3}$ gr.) of the salt. The serum is now measured and divided into two parts, one-third of the amount placed in one tube and the remainder in another. The mercury solution is added to the first part in the proportion of 1 c.c. to each 2 c.c. of serum. A heavy precipitate of albuminate of mercury appears which is completely dissolved on the addition of the remainder of the serum.

"It will be seen that the mixture contains 22 mg. (⅓ gr.) of mercuric chloride in each 7 c.c. At first there was great difficulty in keeping the albuminate of mercury in solution for any length of time, and it was necessary to prepare the solution fresh before each injection; but later it was discovered that if the mixture is heated in the water-bath for one-half hour at 55° C. (131° F.) it will remain in solution indefinitely. It is not necessary to use autogenous serum. Blood may be collected from any individual and the mercurialized serum prepared and kept in sealed ampules.

"The injections are made into one of the veins at the elbow with an all-glass syringe and a 20 gauge needle. * * *

"The initial dose is 1.75 c.c., or 5 mg. (1/12 gr.) of mercury, and is increased to 7 c.c., or 22 mg. (⅓ gr.)."

Nixon[61] has suggested the following modification of Thompson's technic:

"Mercuric chloride, from one-tenth to one-third grain, depending on the dose, is dissolved in 10 c.c. of freshly distilled water and drawn into a 20 c.c. syringe. The needle with syringe attached is introduced into the vein, and 10 c.c. of blood are aspirated into the syringe. The mixture is then injected in the usual manner, without withdrawal of the needle from the vein."

Thompson[62] has again modified this method as follows: "A 2 per cent solution of mercuric chloride or benzoate of mercury is prepared. When an injection is to be made a 20 c.c. Luer syringe is filled to the 10 c.c. mark with sterile normal salt solution and the plunger removed. The dose of mercury is then measured with a graduated pipette and dropped into the barrel of the syringe. The plunger is replaced, and the solution thoroughly mixed, and the air expelled. The needle is then inserted into a prominent vein at the elbow, traction made on the plunger until 10 c.c. of blood have been withdrawn and mixed with the mercury solution, when the entire quantity of blood and mercury is reinjected.

"By withdrawing the blood into the syringe it mixes with the mercury and forms an albuminate which is noncorrosive and does not cause phlebitis.

"The use of salt solution instead of water obviates the danger of hemolysis."

Mercury by Fumigation.—Fournier[63] states that the treatment of syphilis by fumigation is old, and that it was mentioned by Bolognini and Catanée[64] early in the sixteenth century. As to the way in which this was done in the old days Fournier states:

"The old treatment, which was also called 'treatment by perfumes' consisted in preparation, fumigation, and sudation. The preparation, as in the case of inunction, included bleeding, purging, and the use of the so-called alterative and depurative remedies. After this the patient, quite naked, was put in a kind of a small tent in a closed and heated chamber. Near the patient was placed a brazier in which tablets were thrown to produce fumigation. These tablets were of complex composition, and, besides various mercurial preparations, such as cinnabar, calomel, red precipitate, turpeth, etc., contained substances intended to cause a dense smoke, such as fats, resins, incense, mastic, oliban, benzoin, aloes, styrax, etc. The patient was exposed to this hot and smoky vapor for half an hour to an hour, according to his strength. It is needless to say that he emerged in a half suffocated condition. However, if he showed signs of swooning, he was allowed to breathe a little pure air by means of a tube passed into the tent. Finally the patient was put into a hot bed and covered with bedclothes, and left to perspire for an hour or two.

"This procedure was repeated every day or every other day, according to the strength and power of resistance of the patients, for it was no light affair to support such semiasphyxiation."

At the present time fumigation is but little used. When this method is employed the patient is put in a cabinet that leaves the head out, and within the cabinet is placed mercury in a porcelain crucible over an alcohol lamp. This method is not to be recommended as it has no advantages over inunction or injections.

Mercurial Flannels.—In this method flannel is impregnated with mercury in a fine state of subdivision, they being first soaked in a mercurial bath and then in ammonia, so that ammoniated mercury is formed. They are frequently known as Merget's flannels. Blaschko's mercolint consists of cotton impregnated in the same way. They may be worn around the neck, and the vapor inhaled. A piece of flannel 10 by 8 inches is said to give off about $\frac{1}{7}$ of a grain of mercury every hour.

Mercurial Plasters.—It has been believed that not only were mercurial plasters good for the local lesions of syphilis, but that they also might be useful for the general treatment of the disease. The most famous mercurial plaster was the famous emplastrum de Vigo, which according to Fournier[66] was made as follows:

"Oil of camomile, oil of anethum, oil of nard, oil of lily, āā, 2 ounces; saffron, 1 ounce; pig's fat 1 pound; calf's fat, ½ pound; euphorbium, 5 drams; oliban, 10 drams; oil of laurel berries, 1½ ounces; viper's fat, 2½ ounces; living frogs, six; earthworms washed in wine, 3½ ounces; juice from the roots of dane-wort and alder, āā, 2 ounces; odoriferous rush, stoechas, a handful; aromatic wine, 2 pounds. Boil until evaporation of the wine; filter and add: Litharge 1 pound; turpentine, 2 ounces; white wax, q. s. Make a plaster in the form of a sparadrap, adding towards the end of the process 1½ ounces of liquid styrax. Remove from the fire, and agitate the mixture with a spatula till it is half cold. Then add mercury mixed with saliva, 4 ounces. Agitate again with the spatula till the mercury is completely incorporated."

In 1890 Quinquad[67] studied the action of mercurial plasters, and recommended the following:

Diachylon plaster	30 parts
Calomel	10 "
Castor oil	3 "

This is applied to the skin for a week, and then renewed. Quinquad has showed that mercury can be found in the urine, and that secondary lesions will promptly disappear.

Mercurial Baths.—Baths in a solution of mercury were formerly much used in the treatment of congenital lues, but now are but little employed. The formula was as follows:

Bichloride of mercury		
Ammonium muriate	āā	20 gm.
Water		180 c.c.

This mixture is added to the bath, and was doubtless more or less efficacious according to the abrasions of the skin that would

permit of absorption, and according to the amount that was left on the skin so that it could be volatilized and inhaled.

Mercurial Suppositories.—Audrey[68] advocated the use of mercurial suppositories in 1905. They were made of gray oil and cocoa butter, and each contained from 0.02 to 0.04 gram of mercury. They were used daily.

Tests for Mercury in the Urine.—It is sometimes necessary to examine the urine for mercury, either to see whether the substance is being absorbed, or whether there is some still in the system. Wile and Elliott[69] have recently done some work on this problem and recommend a modification of the Reinsch test. In this test concentrated hydrochloric acid is added to the cold urine. In this mixture pieces of copper wire, or better copper dust, are allowed to remain for twelve hours, then the copper is heated in a capillary tube, and the mercury driven off on a bit of gold foil which is held at the opening of the tube, so that an amalgam is formed. By this test as small a quantity as 0.025 mg. per 300 c.c. can be satisfactorily detected.

Zittman's Decoction

Possibly the best of the recent articles upon the old Zittman's decoction is that by Montgomery,[70] who contends that this remedy should be made in the old way. He gives the following directions:

Sarsaparilla root	100 gm.
Water	2600 c.c.

Then add well mixed up and in a linen bag

White sugar	
Powdered alum	āā 6 gm.
Calomel	4 "
Cinnabar	1 "

Allow to stand overnight in a covered porcelain or earthenware vessel. The next morning simmer gently for eight hours. Then add:

Fennel seeds	
Anise seed	āā 4 gm.
Senna leaves	24 gm.
Licorice root	12 "

The seed should first be brayed in a mortar and the leaves should be cut fine. Allow the mixture to stand for three hours and then strain off 2500 grams. This should be labeled Zittman's Decoction (strong).

The weak decoction is made as follows:

Take the dregs left after straining off the strong decoction, and add to them

Sarsaparilla root	50 gm.
Water	2600 c.c.

Boil gently as before three hours, stirring frequently, and add:

Lemon peel	
Cassia bark	
Licorice root	
Short cardamom seeds	āā 3 gm.

Allow to stand for three hours and strain off 2500 grams.

Bottle and label Zittman's Decoction (weak).

The average dose is a wine glassful each of the strong and of the weak; but if this is too laxative, the dose may be reduced. Montgomery considers this a valuable remedy in malignant syphilis, and when either mercury or potassium iodide are badly borne. Fournier[71] is not at all enthusiastic over it. It is probable that the mercury in it is the only drug of any value. Lambkin[72] states that he has seen a few patients improve under its use. When I was younger and more credulous I gave it a trial in several refractory cases, but found it of no value.

Contraluesin

The contraluesin of Richter[73] is a combination of colloidal gold amalgam with salicyl, sozoiodol, quinine and bichloride in an artificial serum. It has been stated by Scharff[74] that the pharmacologic action of gold is similar to that of mercury, but that it is an antidote to the latter, so that mercury can be given in larger doses. It is stated to be rapidly absorbed, and that the various ingredients carry the mercury to various tissues in the same way that the dye stuff in arsphenamine conveys the arsenic. The average dose is 1.5 c.c., which contains 0.15 gm. of mercury. It is to be used simply as a substitute for arsphenamine.

Antimony

Antimony has been used experimentally in syphilis because it has been found useful in sleeping sickness. McWalter[75] thinks that it acts like the various older arsenical compounds, but that it is milder in its effects, not producing optic neuritis. The red sulphide is the most convenient salt to employ. From one to two grains may be given daily for two or three months with occasional intermissions of a couple of days.

Quinine

Both Lenzmann[76] and Napp[77] have recommended the use of quinine when neither mercury nor the iodides have a beneficial effect. They report that some cases have been much helped.

Iodides

Power[78] states that iodine and its compounds were first used in the form of burnt sponge for throat lesions until 1821, when Martini substituted iodine. This same year Biett employed the iodine together with mercury, and in 1831 Lugol used it alone. Williams first used potassium iodide about 1831. However, it was Ricord[79] who really popularized the use of this drug, teaching that it was of the greatest value in the late stages.

The potassium iodide has been the salt most employed, but the sodium, strontium, ammonium and rubidium salts have been advocated. Also iodoform, iothion, iodol and the proprietary remedies, tiodin and iodipin, have been used. The iodides are most frequently administered by mouth. They may be used alone, or in conjunction with mercury, the latter being the well-known mixed treatment, a formula for which has already been given. Potassium iodide is frequently given in saturated solution, the prescription for which is:

Potass. iodidi	100. gm.
Aquæ distill. q.s. ad	100. c.c.

The dose of this varies, some authors recommending very large doses, even as large as several ounces a day, but others, such as Hartzell,[80] believing that smaller doses are just as good. Some give ten drops after each meal in a full glass of water, while

others start with one drop, and increase one drop a day, so that the patient receives three drops the first day, four the second, five the third day and so on until about half a dram is being given at a dose. It should never be given before meals as it is very irritating to the stomach mucosa. It has been claimed that it is better given in either carbonated waters or in milk. It has also been administered intramuscularly in a 50 per cent solution, doses of from four to eight grains being employed. Doevenspeck[81] has used it intravenously, using a 5 per cent solution and injecting 2 c.c. daily. Enemata have also been advocated, 5 grams being dissolved in 200 c.c. of peptonized milk, to which has been added a few drops of laudanum. Iothion has been used by inunction.

There can be no doubt that iodine is not a true treponemacide. Nichols[82] has clearly demonstrated that the amount of iodine tolerated by the body has absolutely no effect upon the organisms of syphilis. However, in experimental work upon monkeys Neisser[83] has shown that it is possible to prevent syphilis if doses of from 7 to 8 grams be employed. In man there is no reason to believe that the tolerated doses have the slightest effect upon early syphilitic lesions where there are many organisms, neither is the Wassermann reaction in the slightest influenced by its administration. On the other hand in the case of late lesions there can be no doubt but that the administration of the iodides will cause resolution in most cases. However, it should always be borne in mind that they are more than prone to appear again as soon as the remedy is stopped. It has, of course, been believed that potassium iodide acts by breaking down fibrous tissue, and it has been recommended that the drug be used before the administration of arsphenamine to late cases, in the hope that the treponemata would become more easily reached by the arsenic. However, Jobling and Petersen[84] have recently explained the action of iodine as due to the destruction of antienzymes. Their statement is as follows:

"Owing to its scarcity we have not been able to examine material from gummata, and so we are unable to state positively that the antienzymes present are similar to those found in tuberculous caseous material, but it is probable that the same agents are active here also as in anemic infarcts in which autol-

ysis does not occur. If this assumption is correct, it is not difficult to explain why large gummata rapidly disappear when the patient is brought under the influence of the iodides. It is due to the fact that unsaturated fatty acid radicals which inhibit autolysis, have become saturated with iodine. As soon as this occurs, the ferments which are present, or which may be brought in, become active, autolysis takes place, and the necrotic tissue is absorbed. Here, also, the local action of the ferments is made less difficult by the reduction of the antienzyme in the circulating blood. It must be borne in mind that the iodides are not as effective in the earlier stages of syphilis when necrosis of tissue is not so evident.

"If the above interpretation of the action of iodine is correct, it gives the clinician a rational idea of what he is accomplishing when he gives iodides to a patient in the tertiary stage of syphilis. According to this view, iodine neutralizes the action of the agents which prevent resolution and absorption of the diseased or necrotic tissue, and at the same time lays bare to the action of the real germicidal agent the infecting organism which previously had been protected by necrotic tissue. With the exposure of the infecting organism, such agents as mercury and salvarsan would be much more effective."

From this work it seems possible that we have a scientific explanation of the action of the iodides and that will be found of great value in the treatment of late syphilis as a preliminary to the giving of either mercury or arsphenamine.

It should always be remembered that the iodides have certain untoward effects. Usually the first symptom of iodism is that of a metallic taste in the mouth, aptly described by Keyes[85] as though a copper cent were held in the mouth. Coryza is liable to follow, and this may be either mild or severe with much discharge and at times pain in the sinuses. Gastrointestinal disturbances are not infrequent, and there may be either slight "indigestion" or severe colicky pains. The skin is frequently affected, the commonest lesion being an iodide acne, which resembles ordinary acne vulgaris. However, the cutaneous lesions may be much more severe and there may be bullae, at times hemorrhagic in character, eczema, herpes or even nodules. Purpura has been described. There may be edema of the upper

air passages, especially of the bronchi. Salivation is rare but does occur. Many men administer arsenic along with the iodides, holding that by them iodism is prevented.

Iodine is absorbed quickly and is likewise rapidly excreted, chiefly by the kidneys, but also through the skin, eyes, and salivary glands.

Arsenic

Herzfeld[86] states that the use of arsenic in combating the ravages of syphilis dates back to the time of Fallopius. Many modern syphilographers have long realized that preparations of arsenic would often have a most beneficial influence upon chronic syphilitic lesions that had resisted the action of mercury and the iodides. The preparations most used were liquor potassii arsenitis (Fowler's solution) and liquor arseni et hydrargyri iodidi (Donovan's solution). Various other forms of arsenic have been employed, some hypodermically, but they have never been popular. However, about ten years ago the first work was done in the use of organic arsenic preparations. Since that time preparation has followed preparation in a rather bewildering succession.

Atoxyl.—Atoxyl or soamin was the first of these compounds to gain any vogue. Chemically it is paramidophenyl sodium arsenate. It was much used hypodermically by certain continental experimenters, a full report of this work being conveniently found in Mulzer's[87] book. While it unquestionably had a favorable effect upon syphilitic lesions, still it had a most disastrous effect upon the optic nerves of some patients, and its use has been entirely discontinued.

Arsacetin.—Arsacetin was obtained from atoxyl by chemical changes. At one time it was used for syphilis but is employed no longer, it having the same objections that atoxyl has.

Hectine.[88]—About 1912 many of the French observers were reporting brilliant results from hectine, which is benzolsulphone-paraminophenylarsenate of sodium. We no longer hear about it.

Soamin.—Soamin was first employed in England in 1907. It is a sodii p-aminophenylarsonas and is supposed to be without toxic secondary effects. It is now marketed by Burroughs Wellcome & Co., and has been greatly recommended by some men, but certainly does not compare with arsphenamine.

Arsenophenylglycin.—This substance has a strong parasitotrophic action and was formerly recommended by Ehrlich as a therapia sterilisans magna, because he hoped that one injection would kill all parasites. However, there were severe untoward effects, chiefly cutaneous eruptions, emaciation and various nervous manifestations.

Sodium Cacodylate.—Chemically sodium cacodylate is dimethylsodiumarsenate. In 1910 Murphy[89] extolled it as an antisyphilitic, and even more recently he seemed enthusiastic about it,[90] an enthusiasm that most men can not accept.[91, 92] It is extremely difficult for me to understand how any man can prefer sodium cacodylate to arsphenamine in view of the experimental and clinical data that now exist. While the former may give good results if used in large doses, and doses of great size[93] are well borne by almost all patients, still arsphenamine is unquestionably superior.

Venarsen.—Venarsen, which is now being advertised extensively, is nothing but sodium cacodylate with mercury biniodide and sodium iodide. It has been rejected by the Council on Pharmacy and Chemistry of the American Medical Association.[94] There is not the slightest excuse for its use.

Arsphenamine

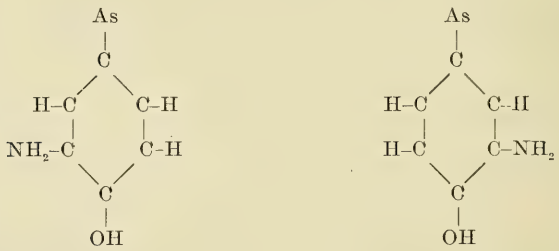
The introduction of salvarsan raised the greatest medical furor of recent years, possibly because it was so extensively advertised, and advertised is the only correct word to describe the propaganda that was carried on in the medical and lay press. Ehrlich saw fit to patent the preparation, ostensibly in order to protect the public against improperly prepared substitutes. Certainly his fame would have been greater had he followed the example of many other illustrious investigators and given the remedy to mankind! This war has well shown the evils that may be attached to the patenting of an important medicinal preparation.

History.—Arsphenamine was the result of much painstaking and careful work, work that was conceived of a great idea and born of much labor. The work was founded on the idea that there exists a drug that will have a specific chemical affinity for

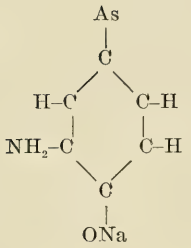
a parasite and not for the host. Arsphenamine was the six hundred sixth drug tested, hence its famous name "606."

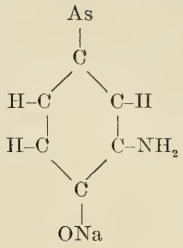
During the winter of 1909-10 the therapeutic effects of arsphenamine were first tried. It was soon found that in animals the curative dose was much less than the tolerated dose. Hata's work[95] showed that in mice with recurrent fever the ratio of the tolerated dose to the curative dose was as 2.7 to 1, and that in rats the ratio was as 3.3 to 1. In chicken spirillosis the ratio was as 58 to 1, while that of atoxyl and the similar drugs was as 2 to 1. In syphilitic rabbits the ratio was determined to be not less than 7 to 1. As soon as the animal experiments were completed Ehrlich had the preparation tested upon man by Alt of Uchtpringe. The injections were first made intramuscularly and the clinical results were sufficiently encouraging to warrant further work. Schreiber of Magdeburg was the first to use arsphenamine in cases of recent syphilis, and the reports were so good that experimentation upon a large scale was begun. Wechselmann was one of the first to work on a large scale, but he was closely followed by many other observers. Since those early days the use of arsphenamine has steadily increased.

Composition.—The following account of the chemistry of arsphenamine is derived from McDonagh.[96] Salvarsan is the commercial name given to dioxydiamidoarsenobenzol, whose formula is:



Inasmuch as this body is insoluble in water the dihydrochloride salt was prepared. This has the same formula as the above except that HCl is attached to the NH_2. This preparation dissolves in water but is strongly acid and is toxic so sodium hydrate is added at the time of mixing, when the formula becomes as follows:





Puckner and Hilpert[97] have written a valuable article on these chemical changes. The arsenic content of arsphenamine is 31.56 per cent.

Action of Arsphenamine.—It is usually assumed that arsenic is the substance which is responsible for the death of the treponemata, for these organisms in vivo promptly die when brought in contact with the drug, as has been proved time and again. There can be no doubt but that arsenic is excreted unchanged, that is in the trivalent form, from persons who have received the drug. McDonagh[98] states that the arsphenamine may be expected to act in one of the following ways:

1. The basic portion takes up the acidic phases of the organism.
2. The acidic portion takes up the basic phases of the organism.
3. The catalytic action of the arsenic destroys the organism by oxidation.
4. Arsphenamine is also a reducing agent and may exert action in this direction.

Ehrlich[99] believed that in the protoplasm of the parasites there are certain chemical groups which are capable of combining with certain chemical groups in arsphenamine and he thought that the drug worked by virtue of its arsenic and orthoaminophenol receptors. McDonagh[100] states: Salvarsan becomes attached to the lipoid-globulin molecules of the syphilitic parasite, the plasma cells, and the serum, by virtue of its amino groups and of the peculiar physical properties of protozoal lipoid-globulin. It attacks these phases of the Leucocytozoon syphilidis in which reaction is most marked, especially the spirochaedal phase, in virtue of its free hydroxyl groups.

"The arsenic acts as a catalyst, that is to say, it accelerates the complementary or oxydase action of the lipoid-globulin (anti-

body) of the serum, which destroys the parasites by means of adsorption."

Fate of Arsphenamine in the Body.—Wechselmann[101] states that in the organs of a patient brought to autopsy fourteen days after the intramuscular injection of arsphenamine no arsenic could be demonstrated although it could be found in the muscle. After the intramuscular injection arsenic can be demonstrated within forty-eight hours in the blood, but it disappears by the fourteenth day. At the same time it can no longer be demonstrated in the urine and feces. It first appears in the urine within an hour after an intramuscular injection. Arsenic is eliminated by means of the kidneys and bowel. A further bibliography is given by Wechselmann.

Toxicologic and Pharmacologic Testing of Arsphenamine

By Jay F. Schamberg, M.D., Philadelphia, Pa.

Dioxydiaminoarsenobenzol dichlorhydrate, commonly known as arsphenamine, is the most complex compound employed in medicine. Before its final elaboration, numerous processes must be passed through and a considerable number of chemical substances used. The purity of the final compound is naturally influenced, to a very large degree, by the purity of the various intermediate products. If these exhibit variations, the ultimate product will likewise do so. Unfortunately arsphenamine can not be purified by repeated crystallization. It is precipitated by ether out of a methyl-alcohol-hydrochloric acid solution of the base, and in this precipitation, traces of other substances may likewise be thrown down. Arsphenamine, particularly when prepared commercially, will exhibit variations in different lots. It may be accepted almost as an axiom that a substance which is not of absolute chemical purity can not be expected to exhibit constancy in biological effects. Unfortunately the chemical variations in arsphenamine can not be adequately determined by chemical analysis, but only by experiments upon animals, and by the results obtained from its use in man.

The value of any medicament designed to kill germs within the living body, is determined by the relation of its lethal dose to its curative dose. If the curative dose be the same or but

slightly lower than the fatal dose, then the drug is of relatively little value. The greater the latitude between the fatal and the curative dose, the safer and consequently more valuable is the remedy. Arsphenamine, on account of the complexity of the molecule, and the multiplicity of processes through which it must pass before its final elaboration, will exhibit variations both in toxicity and in therapeutic effect. The former can readily be demonstrated by determining the fatal dose in animals. The latter may be determined by employing the drug in experimental infections in animals, and by noting the effects in man. If we admit the existence of variations in toxicity, variations in therapeutic effect must be accepted as a logical corollary, for the former indicates an enhancement or a lessening of the affinity for the body cells, and the latter, modifications of affinity for the parasite. Otherwise expressed, variations in therapeutic effect mean variations in toxicity for the parasite. The slightest changes in the chemical constitution of a compound may influence its selective combining power with cells and with parasites.

From what has been stated, it is obvious that before arsphenamine (no matter under what trade name it is marketed) is released from the laboratory, it is essential that tests as to toxicity and therapeutic effect must be carried out.

The toxicity tests which were adopted by Ehrlich and which have been routinely employed with salvarsan, consisted in the subcutaneous injection of a solution in mice. In the circular of instructions accompanying salvarsan ampules, we read "Only such salvarsan is supplied of which the dose tolerated by mice injected subcutaneously amounts to 1 c.c. $\frac{1}{125}$ up to a maximum of $\frac{1}{150}$ per 20 grams of live weight." This would represent the equivalent of 32.5 mg. to 40 mg. per 100 grams of rat weight, or 325 to 400 mg. per kilo. While the salvarsan made under the personal supervision of Ehrlich and Bertheim might have been of such purity as to be tolerated in this dosage, that which has been prepared commercially, and has been purchasable in the open market, does not live up to such tests.

My colleagues, Drs. Kolmer and Raiziss, and I (*Journal Cutaneous Diseases,* May-June, 1917), have shown that the German salvarsan tested by us by subcutaneous injections in mice, was never tolerated in the dose of 40 mg. per 100 grams of rat weight,

Dr. Kolmer has shown that the size of the infecting dose is of importance in influencing the period when the parasites first appear in the blood stream, the duration of life, and the degree of effect of parasiticide remedies. A given number of trypanosomes, say from 120,000 to 180,000, is injected. (The count is made somewhat after the manner of a red blood cell count.)

Parasites appear in the peripheral blood in from twenty-four to forty-eight hours. A drop of blood taken from the tail examined on a slide under the microscope readily reveals the presence of trypanosomes.

Twenty-four hours after infection, the medicament to be tested is injected. It is practically impossible to give intravenous injections to white rats without cutting down and exposing a vein. Injection may be given into the caudal vein, but will be successful in only a proportion of the cases. The most satisfactory method is to expose the jugular vein and inject the drug into this vessel.

The sterilizing or curative dose of arsphenamine should be in the neighborhood of 1.5 mg. per 100 grams of rat weight. One will find that with doses below this, the blood will remain sterile for a number of days, but then the parasites will begin to appear, and in the course of four or five days will increase so rapidly as to destroy life. Before death, in experimental trypanosomiasis, the number of the parasites in the blood exceeds the number of red blood cells.

If the strain of trypanosomes be quite virulent the requisite sterilizing dose may be larger. Transmitting the infection rapidly from one animal to another may bring about such enhancement of virulence. One must likewise avoid developing an arsphenamine fast strain, as has occurred several times in our laboratories.

The ultimate and final therapeutic test of any agent is of course its use in the disease for which it is intended. We obviously would not employ human beings for purposes of testing medicaments, but after the particular product has been adequately tested for toxicity and for curative properties on animals, valuable data may be secured by careful notes concerning reactions or absence of reactions in the human species.

Different lots of arsphenamine will vary and some are better than others. Some will give rise to a much larger incidence of reactions than others.

One group of reactions is characterized by vasomotor phenomena developing during the course of the injection or immediately thereafter. One or several of the following symptoms in varying degrees of severity may be noted. Flushing of the face, injection of the conjunctivæ, puffing of the eyelids and lips, nausea, vomiting, cyanosis, followed by pallor and syncope; in rare cases convulsions, and still more rarely, death.

There are many causes of the reactions following the use of arsphenamine, such as the endotoxemia from the rapid destruction of spirochetes (Neisser), bacterial protein in the water (Wechselmann), absorption of broken down cell products (Luitheln and Mucha), etc. These causes are responsible for some of the febrile and gastrointestinal reactions. The vasomotor reactions above referred to, however, we believe to be due to an impurity in the drug. We have made earnest endeavors to identify the chemical nature of this impurity, but thus far without avail. For convenience of reference, it is permissible to refer to this impurity as substance X.

We are convinced that certain serial products contain a relatively large amount of substance X and others little or none. Among hundreds of serial products of our own arsphenamine (arsenobenzol) we selected, for study, two, because one gave a rather high incidence of "flushing reactions," and the other gave none at all. I have given several hundred injections in the human species with the latter, employing full doses under varied conditions, and have never noted a particle of flushing. This product contains no substance X.

The general experience of physicians, I am sure, will corroborate this thesis. I know that a certain lot of the German product was abandoned by a prominent specialist because of the high percentage of reactions induced. Other lots gave excellent results.

Arsphenamine is a remarkable drug and represents a great advance in medicine. Despite the fact that this particular molecule is remarkably adapted to the destruction of the spirocheta

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Arsphenamine is a remarkable drug and represents a great advance in medicine. Despite the fact that this particular molecule is remarkably adapted to the destruction of the spirocheta

pallida, it is possible that some further modification of it may lead to even superior therapeutic results.

Contraindications for Arsphenamine

When arsphenamine was first introduced Ehrlich warned that it should not be used in cases of fetid bronchitis, debilitated condition unless directly due to syphilis, in cases of disease of the circulatory or nervous organs or in cases of disease of the optic nerve. Pregnancy and high blood pressure were likewise considered as contraindications for its employment, as were nephritis and tuberculosis. At the present time this list has changed considerably. One no longer hesitates to employ arsphenamine in disease of the circulatory system or in syphilis of the central nervous system, in fact quite the opposite is the case. In cases of tuberculosis the drug does not seem to do any harm, and it certainly can help the syphilis. In cases of acute nephritis one would naturally hesitate to use it, for it frequently does temporarily irritate the kidney, as shown by the presence of red blood cells and of an increased amount of albumin, however, in chronic nephritis it can be used sparingly, and if the condition be immediately and not indirectly due to syphilis great good may be accomplished. It is probable that the phenolsulphonephthalein test should be employed before and after using in these cases. Pregnancy is now accepted as an indication rather than as a contraindication for the use of arsphenamine. However it must be remembered that there are some individuals who do not tolerate it well; with each injection there may be an increasing general reaction and a loss of weight: in such patients the drug should be temporarily discontinued; fortunately such cases are very rare, although they do occur. Wechselmann[102] warns that in early cases of congenital lues where there are present enormous numbers of organisms, the employment of arsphenamine may cause death through the setting free of great quantities of endotoxins; however, we no longer hear of this danger. Recently Fordyce[103] has given one very pertinent warning. He states: "In cases where a dermatitis has been present the drug should not be repeated within six months or a year. I have seen death follow in a patient where the significance of

such a rash was disregarded during intensive treatment with neosalvarsan. The injections were continued and a most extensive exfoliative dermatitis developed, ending fatally." The character of the rash against which Fordyce warns may be either purpuric or erythematous.

Untoward Effects of Arsphenamine.—It can not be too strongly emphasized that a sharp distinction must be drawn between the effects of arsphenamine before and after absorption: also an equally sharp distinction must be drawn between the drug properly prepared and administered and one improperly prepared or administered.

1. **Local Reaction.**—Arsphenamine is very irritating to the tissues: when given subcutaneously or intramuscularly a certain amount of reaction always results: when given intravenously with some leakage into the periphlebitic tissues a local reaction is constant. As to the nature of the substance causing this inflammatory reaction there has been some discussion, many men contending that it is due to the character of menstrum: however, that this can not be due is proved by the fact that no matter what this menstrum is there is always reaction. Further comments upon this point will be found in the sections devoted to the administration of arsphenamine.

2. **Febrile Reaction.**—When arsphenamine was first administered it was usual to find that there was a sharp rise of temperature in many cases and that a chill sometimes resulted. Martin[104] has gone so far as to say that these reactions are due to the liberation of endotoxins from killed organisms, and Swift[105] is inclined to take the same view. However, as febrile reactions have steadily decreased as the skill and experience of the operator has increased I can not accept this opinion. At the present time it is unusual for me to get a rise of temperature amounting to more than one-half a degree except the first injection in the florid cases. As bearing upon this point the question of the distilled water must be discussed. When we were less careful as to quality of the distilled water that we employed reactions were much more frequent than they are at present. While the water was always sterile still a reaction was the usual result, and it was blamed upon the arsphenamine. To Wechselmann[106] belongs the credit of pointing out that in distilled water there could usually be

found the remains of numerous dead organisms, which are so apt to contaminate standing distilled water; he further showed that endotoxins were released from these organisms when they were killed by boiling and that these endotoxins caused many reactions. This point is extremely important, for dispensers have found that they will sometimes get precipitates with drugs which should not precipitate, surgeons have found that injections of saline solution will give rise to unpleasant after-effects, and it is well known that toxic effects can be produced in animals by the injection of distilled water alone. Hence this discovery of Wechselmann's is not alone of importance to the syphilologist. Also there can be no doubt but that the quantity of water employed has a considerable influence. When I first used neosalvarsan I employed 200 c.c. of fresh distilled and double boiled water; there was often considerable reaction, but when the quantity was reduced to 20 c.c. there was usually no reaction. It is possible that the tonicity of the solution should be taken into consideration and that the injection should be made as nearly isotonic as possible, even though the rate of injection into the blood stream be very slow. The temperature of the water employed is also of importance: Schamberg tells me that he gets less reaction with arsenobenzol when he employs cool water than when he employs water at blood temperature or higher. Likewise the question of the neutralization of the acid salt is important, for MacKee[107] has clearly shown that if this be not neutralized there is grave danger of a serious reaction or even of death. On the other hand the addition of too much sodium hydroxide has been shown experimentally by Schamberg[108] not to be attended with danger, unless that of local irritation to the vessel wall. In the past there has been the very distinct feeling that if the arsphenamine were oxidized, either in the ampule or in solution, it was very dangerous. Again, Schamberg has shown that this is true only to a limited extent, and that slight oxidation does not render the injection more dangerous.

3. **Immediate Reaction Following Administration.**—The commonest immediate symptoms are those that show symptoms of vasodilatation or vasoparesis. This symptom-complex may occur either during the administration of arsphenamine or immediately

thereafter. The patient usually first complains of an unpleasant taste in the mouth, then the voice becomes thick and the fingers and perhaps the toes begin to tingle. First an injection of the conjunctivæ is noticed and then the face flushes. Precordial distress may be complained of, although this is by no means usual. The pulse usually becomes rapid and weak. Unquestionably certain preparations of arsphenamine give rise to these symptoms more commonly than do others, and also there are certain patients who are more apt to give these reactions than do normal individuals: I have had under my care one woman who could take no preparation without such a reaction; in such cases the question of anaphylaxis must be thought of. Schamberg considers that the reaction is due to an unknown poison in the arsphenamine, which he calls substance X. However, such reactions seem to be more common in the hands of some men than in those of their confreres, even though the same preparations be used. Hence there must be three factors, first, the drug used, second, the patient, and third, the preparation of the drug. Occasionally there may be intense abdominal pain accompanied by a moderate amount of collapse. In some exceptional instances vomiting may occur during the injection. Fordyce[109] considers that a psychic element is probably present in most of these cases. Fordyce also mentions severe pain in the lumbar region as a possibility. Schamberg considers this due to a vasoparesis in the kidney. In the cases where there were marked evidences of vasodilatation the subcutaneous or intramuscular injection of adrenalin will usually give almost immediate relief.

4. **Intermediate Reactions Following Administration.**—Every physician who has employed arsphenamine has realized that in from two to twenty-four hours certain unpleasant symptoms might supervene. These are headache, general depression, nausea and vomiting and diarrhea, sometimes accompanied by intestinal pain. In addition there is frequently some elevation of the temperature and chills. A toxic erythema occurs in some cases. There may be any grade of reaction from one so slight as to be almost imperceptible to one that totally incapacitates the patient for forty-eight hours. Unquestionably technic has much to do with many of these symptoms, and as our experience has increased the number and severity of these reactions have de-

creased. At the same time there are certain persons who always react more or less severely. Undoubtedly the preparation used also plays a great part. One form or even one lot of arsphenamine may give the same patient much more reaction than does another form or lot of the drug. In other words some preparations are more toxic than are others. Unquestionably if the patient will see to it that his bowels are thoroughly opened, if he will eat but lightly, and if he keep quiet after the treatment the reaction is not so prone to be severe.

5. **Delayed Reactions Following Administration.**—Reactions coming on several days after injection are always to be viewed seriously, and another injection should not be given until at least six months have elapsed, especially if there be any cutaneous manifestations, as evidenced by a dermatitis or a purpura. These delayed symptoms may be gastrointestinal, or there may be malaise or jaundice. At times there is evidence of considerable kidney irritation. Other observers have reported encephalitis.

6. **Lesions of Various Organs Caused by Arsphenamine.**—*The Kidneys.*—While as a general rule the kidneys are not so much affected by arsphenamine as they are by mercury, still even apparently normal kidneys may show traces of considerable irritation: for instance it has been repeatedly observed that red blood cells may be found in the urine a day or two after its administration. At times, in case of an albuminuria, the amount of albumin may be considerably increased. Rarely almost complete anuria may be noted several days after its administration. The experimental work of Pearce and Brown[110] shows that in dogs the administration of arsphenamine, neoarsphenamine or galyl may cause distinct lesions; they state: "The type of kidney produced by injections of these drugs falls into the general class of red kidneys, although certain differences relate them to the other main type, the pale kidney. The differences consist in a relatively greater degree of tubular necrosis and in the character of the vascular injury. This group of kidneys, as shown by the arsphenamine and neoarsphenamine kidneys, shows a considerable amount of necrosis of the cortex which is most conspicuous in the inner half. On the other hand, although the kidney is

reddened throughout, the congestion and hemorrhage are most prominent in the outer half of the cortex and the inner portion of the boundary zone.'' It is only fair to state that they usually employed doses approaching the lethal ones.

The Adrenals.—Brown and Pearce[111] found that toxic doses of any of the arsenic compounds including arsphenamine and its allies produce definite changes in the adrenals of guinea pigs, these changes comprising congestion, hemorrhage, disturbances in the lipoid content, cellular degenerations and necroses, and reduction in the chromaffin content. They suggest that the therapeutic content of arsphenamine may cause adrenal stimulation. It is possible that certain of the fatal cases may be due to adrenal destruction.

Liver.—Ormsby states:[112] ''When jaundice supervenes, involvement of the liver has occurred, due, as most observers believe, to a direct action of the arsenic on the liver cells.'' This subject has been very carefully studied by Milian,[113] who gives a complete bibliography to date. Milian states that in 2125 injections he has observed this condition 17 times. He finds that jaundice usually does not appear until about two months after treatment, or about the same time that neurorecidives appear. He remarks that it usually develops in those who have received insufficient treatment, so it is possible that not the salvarsan but the disease may be responsible. He further reports that in several cases the jaundice was cured by additional injections of salvarsan.

Encephalitis.—Unquestionably the most serious consequence of arsphenamine is the production of encephalitis, which is responsible for about three-fifths of all arsphenamine fatalities according to Meirowsky and Kretzmer.[114] Leredde and Jamin,[115] as well as Ormsby,[116] state that encephalitis has been thought to be due to three separate conditions, first to arsenical poisoning, second to intolerance, and third to a Herxheimer reaction. Ormsby concludes that is is probable that the Herxheimer reaction is responsible, although he recognizes the fact that the primary toxicity of arsphenamine may be the cause in some exceptional instances. Leredde and Jamin have studied the question very thoroughly and conclude that the Herxheimer reaction is the true cause. Inasmuch as various observers, especially Leredde,[117] have shown that it is usually the first injection that

causes the trouble, it at once becomes evident that anaphylaxis can be ruled out. It has been found that encephalitis is more frequent after large doses of arsphenamine than after small doses, and that in certain instances death has followed where the injections have been closely repeated. The symptoms of encephalitis are usually those of unconsciousness with epileptiform attacks and death. In the cases examined postmortem it has been usual to find syphilitic lesions in the central nervous system.

Neurorecurrences.—Shortly after arsphenamine made its appearance various observers began to report that paralyses of the cranial nerves were more than prone to follow its administration. Of course it was promptly recalled to mind that arsenic had a destructive action upon various nerve tissue, especially the optic nerve and for a time it was feared that we were going to have the same experience with arsphenamine. Ehrlich turned over the solution of the question to Benario,[118] and he shortly published a most admirable monograph, in which he showed that the recurrences only occurred in those patients who had received but one or at the most two injections, that the spinal fluid gave evidences of syphilis, and that the lesions really occurred at the point where the nerve passed through the bony wall, and where compression from inflamed meninges would naturally cause trouble, and lastly he showed that additional treatment with arsphenamine would cause the disappearance of the trouble. Hence it is quite definite, for these views have received general confirmation, that neurorecurrences are due to syphilis and not to arsphenamine.

Cutaneous Lesions.—McDonagh mentions both crops of boils or furuncles and also herpes simplex as sometimes following arsphenamine therapy. I have had two cases where a mild eczema developed in the flexors after each injection. However the most serious lesion is of the toxic type, and this may be purpuric, it may resemble erythema multiforme or urticaria, or it may be desquamative, similar to dermatoses caused by mercury and various other drugs. In all instances the latter rashes should keep the physician from administering arsphenamine to the patient for a period of at least six months.

7. **The Jarisch-Herxheimer Reaction.**—This reaction consists in the exaggeration of the pathologic and hence the clinical processes following the administration of antisyphilitic medication. It is much more frequent after the use of arsphenamine than after mercury and by Wechselmann,[119] Gennerich[120] and others is believed to be due to a liberation of endotoxins from the treponemata killed by the arsphenamine. Clinically it is noted that the lesions become of a brighter color and that some swelling usually takes place. When this occurs in the brain unpleasant results may ensue as has already been noted in the section on encephalitis.

Arsphenamine Fatalities.—There is a large amount of literature dealing with deaths following the administration of arsphenamine.[121] Leredde has been particularly active in collecting statistics upon this point. He gives the following figures, which undoubtedly do not give a sufficiently high report for deaths, inasmuch as many have been concealed.

YEAR	NUMBER INJECTIONS	DEATHS
1910	50,000	16
1911	800,000	92
1912	1,280,000	66
1913	2,000,000	37

In general the literature would seem to show that in the majority of instances death has followed either the first injection, or a later injection only when this followed very closely upon the first, or when some severe reaction caused by the first was disregarded. It is interesting to note that in general the French school have been inclined to blame the arsphenamine itself for the deaths which followed its administration while the German school has held that either improper selection of cases, improper technic or coincidence would explain most of them. Thompson,[122] in his late book, states that death may be due to sepsis, to air embolism, to embolism from fibers of cotton, to a faulty preparation of the drug, as failure to neutralize, and from the use of the remedy upon patients who were suffering from such severe lesions of the viscera that they should not have received it, except perhaps in very small doses. However, there can be no doubt but that the majority of the deaths are due to

hemorrhagic encephalitis or myelitis, and at the present time the general tendency is to blame the arsphenamine directly for these deaths, it being held by many observers that a Herxheimer reaction is at the bottom of the trouble. A number of years ago Wechselmann[123] propounded the theory that in the majority of instances death occurred following dosage with mercurials and that these mercurials had damaged the kidneys to such an extent that they could not stand the action of arsphenamine. However this view has never gained any acceptance whatever, all facts seeming to disprove it. The work of Brown and Pearce[124] would seem to show that in certain instances death may result from degeneration of the adrenals. If death be due to a Herxheimer reaction the safest method of procedure would seem to be to kill off the treponemata gradually, either by the use of mercury or by the administration of small doses of arsphenamine before beginning with large doses.

In addition to the references already cited the following may be cited: Frühwald,[125] Meirowsky and Kretzmer,[126] Schmitt,[127] and Ormsby.[128]

Clinical Results from Arsphenamine.—In general it may be said that the immediate clinical results from the drug are excellent and often surprising. The treponemata will disappear from a lesion in the course of a very few hours, and the lesions will often heal very rapidly; this is especially true of mucous patches and of nonindurated chancres. It is not at all unusual to find mucous patches that have resisted the action of mercury for months disappear within forty-eight hours after an injection of arsphenamine. The nonindurated cutaneous lesions often disappear within a few days, and even the indurated papules usually begin to resolve by the end of a week. Visceral lesions often do very well, and even nervous lesions may show marked improvement after several injections. When arsphenamine was first marketed various physicians, many of them who were not syphilologists, reported how marvelous this action of the new drug was. Now, as a matter of fact, injections or inunctions of mercury will sometimes give results that are almost as rapid, but there is this difference: on the average, arsphenamine works at least three times as rapidly as mercury, and is much more certain in its effects; in addition its effects upon mouth

and throat lesions are infinitely better. There is now a unanimity of opinion among syphilologists that arsphenamine is far and away our most efficient drug in the treatment of lues. The question as to the radical cure of syphilis will be taken up shortly. One fact about it must always be borne in mind, namely, that it will render infectious lesions organism-free in the course of a few hours; from a public health standpoint this is of the utmost importance.

Serologic Results from Arsphenamine.—The literature is deluged with reports upon the Wassermann after the administration of the drug. In 1912 Howard Fox[129] compiled the results of nearly twenty observers in about 1200 cases and found that the complement-fixation test became negative in from 8.8 to 100 per cent, depending upon the intensity of the treatment: the average was 47.4. However, it must be remembered that these reports were published in the days when it was unusual to give more than one or two injections. In 1914 Heidingsfeld[130] reported 326 cases which were treated solely with arsphenamine with 74.14 per cent negative reactions resulting. Noguchi[131] complains that serologic reports after treatment are very difficult to interpret. While treatment varied considerably Noguchi gives the following statistics as to negative results:

	ONE WEEK	TWO WEEKS	THREE WEEKS	FOUR WEEKS	FIVE WEEKS	SIX WEEKS	SEVEN WEEKS	EIGHT WEEKS
Primary		1	1	2		1		
Secondary			3	5	3	2	1	
Tertiary		2	3	4	2			
Latent			2					
Congenital						1		
Cerebrospinal								
Tabes			1					
		3	10	11	5	4	1	

Craig[132] has given the following conclusions:

1. The best results, as regards the disappearance of the reaction, are obtained in the treatment of patients in the primary stage of syphilis, and the poorest in the treatment of those in the tertiary stage.

2. The reaction, in our experience, has disappeared most frequently during the second, third and fourth weeks after treatment with arsphenamine.

3. The reaction disappears most rapidly in patients treated during the primary stage.

4. The prognosis, as regards the disappearance of the reaction, is most favorable in those patients giving a plus-minus reaction and least so in those giving a double-plus reaction.

5. As regards the method of the administration of arsphenamine, the best results have been obtained from intramuscular injections, and the poorest from intravenous injections. However, in justice to the latter method, it should be stated that a vast majority of the cases were given only one intravenous injection.

6. The data would appear to indicate that at least three or four intravenous injections of arsphenamine are necessary in order to cause the disappearance of the reaction in from 70 to 80 per cent of patients.

7. The complement-fixation reaction disappears more promptly after the intravenous injection of arsphenamine than after the intramuscular.

8. A larger proportion of negative results was obtained in patients previously treated with mercury than in those not so treated, but the time of the disappearance of the reaction was little affected.

9. The great superiority of arsphenamine over mercury, as a specific remedy, was shown in the rapid disappearance of the reaction, after one or two injections of the drug, in patients previously treated for one, two, or three years with mercurials, and in whom the reaction was still positive.

My own results have been practically identical with those of Craig. If the infection has not persisted for more than two months the reaction will usually become negative after two intravenous injections, administered at seven-day intervals, and few cases will remain positive after four injections. In cases that date back for years it will occasionally be found that one injection will convert a positive into a negative, but as a general rule from three to six injections and often more are needed. Some cases, presumably those with foci in the central nervous system or the viscera will resist six or even twelve injections, and even when these patients are made Wassermann-free they are very prone to relapse.

Administration of Arsphenamine.—The drug is usually administered by injection, either intravenous or intramuscular, or more rarely subcutaneous, but it has also been used by mouth and by rectum. Unquestionably in the hands of most men the intravenous method is usually chosen.

Subcutaneous Administration.—It is difficult to see why the subcutaneous method of administration was ever advocated, for every physician who has used a hypodermic injection should know that drugs are not so well absorbed from these tissues as from the muscles, and also that they are much more subject to irritation. Nevertheless at first arsphenamine was extensively employed subcutaneously, chiefly by Wechselmann, Michaelis and Kromayer. Either an alkaline or a neutral solution was prepared and about 20 c.c. was administered beneath the skin of the shoulder blades. As to the technic of these early preparations the books of Mulzer[133] or Wechselmann[134] may be consulted. The results were usually disastrous, for large necrotic areas frequently formed at the site of injection, and the pain immediately after and following the injections was very severe. This method is no longer employed.

Intramuscular Injection of Neutral Solution.—The intramuscular injection of arsphenamine has almost been displaced by the intravenous method, even though it has been claimed by some serologists that better serologic results follow the former method. The reason for this has been the amount of pain and discomfort that the patient has experienced as well as the abscesses that sometimes result. So far as I know Sutton[135] is the only syphilologist of experience who prefers the intramuscular route. His technic is as follows: "All instruments and utensils, and a 4 per cent sodium hydrate solution are sterilized by heat. * * * The salvarsan is dissolved in 6 c.c. of sterile water by the aid of rough-surfaced beads. Four drops of a 1 per cent alcoholic solution of phenolphthalein are placed in the mixture to serve as indicator, and the sodium hydrate solution is then added, drop by drop, with a small pipette, meanwhile vigorously shaking the mixture, until the resulting mixture is slightly but permanently pink in color. The mixture is then drawn into a 10 c.c. all-glass syringe, and the injections immediately made.

"Care must be taken to place the dose properly in the middle of the muscle mass. There is commonly some lumbago-like pain for a few days, but if the dose is properly prepared and injected this is seldom great enough to incapacitate the patient for ordinary labor. The main points to be considered in preparing the drug for injection are slight alkalinity (for this reason a 4 per cent NaOH solution is preferable to the 15 per cent generally recommended) minimum bulk, and absolute cleanliness. The solution is injected in the lumbar region, the dose being equally divided between the two sides."

It seems to me that one serious objection to this method is that it will be impossible by it to give six or eight injections at short intervals, in the way that we like to do in the attempt to get a radical cure. On the other hand in persons suffering from serious organic lesions the drug is absorbed much more slowly, and there is less danger of toxic disturbance. It should always be remembered that the pain resulting from intramuscular injection may be very severe, and the majority of patients refuse to take another injection by this method. Personally I do not use it except in very exceptional instances.

Intramuscular Injections of Oily Suspensions.—Suspensions of arsphenamine in oil have been recommended by various men, notably Kromayer,[136] Levy-Bing and Lafay[137] and myself.[138] Personally I have entirely discarded this method because I found that local trouble might result,[139] even after the lapse of one year. After considerable experience with it I advise strongly against its employment. However it should be mentioned that I have used the Hynson, Westcott and Dunning preparation in cocoa butter with considerable success in many cases in children.

Intravenous Injections.—It is now generally conceded that the intravenous route affords the most practicable method for the administration of arsphenamine. When once learned, the technic is simple, the patient suffers but a trifling amount of discomfort, the drug can be administered as often as is necessary, and the therapeutic results are excellent.

It would be a matter of considerable interest to trace out the development of this method, but this has already been described in detail by Mulzer so is unnecessary here.

The following things are necessary: a supply of freshly dis-

tilled sterile water, a bottle of 15 per cent solution of sodium hydroxide, a sterile funnel with gauze for filtering the solution, a graduated container to which is attached three feet of small bore rubber tubing with a bit of glass tubing inserted near the lower end and a needle, a tourniquet, sterile gauze or sponges and tincture of iodine and alcohol.

1. *Water.*—The water should be freshly distilled on the same day that it is used, and should be twice boiled with complete cooling between the boilings or else autoclaved. It is usually stated that the still should be of glass, but in our work we have not found this necessary. The dilution of the arsphenamine is of importance: it is probable that the solution should be as near isotonic as possible, and this means that to each one-tenth of a gram about 17 c.c. of sterile water should be added. Normal salt solution is not necessary; there is no more reaction or hemolysis from a solution thus made than from one made from normal saline solution. As regards the temperature it is probable that a temperature of about 70° Fahrenheit gives even less reaction than does a warmer solution. If too cold a solution be used, or if too much cool water be run into the veins the patient may complain of cold extremities.

2. *Preparation of the Arsphenamine Solution.*—Ordinarily we prepare a large and a small flask of water; the smaller containing about 30 c.c. of water. A tube of arsphenamine is then washed off with alcohol, and opened with a sterile file; the contents of the ampule are then poured into the flask and shaken vigorously until completely dissolved. Glass beads are totally unnecessary. Then drop by drop a solution of 15 per cent sodium hydroxide is added until a heavy white precipitate forms. The addition of the alkali is slowly continued, constantly agitating the flask until the precipitate disappears and a clear solution results. This solution is best filtered through a bit of gauze, not cotton for fear of fibers, into the container for final use.

The Apparatus for Injection.—The apparatus for injection must consist of a graduated container of at least 100 c.c. capacity: this must be clean and sterile. Attached to the lower end of this is small bore rubber tubing, small bore because there is less danger of air bubbles and because not so much solution is contained in it, a piece of glass tubing is inserted near the

needle end so that air bubbles can be watched for, and so that the color of the solution can be watched, and also so that one can see promptly in case any blood backs up into the tubing. As to the needle, platinum-iridium or gold ones are usually preferred, but we have found that steel ones are perfectly satisfactory if they are thoroughly cleaned after each injection and kept in alcohol. They should be of about 18 gauge, depending to some extent upon the size of the veins, and the point should not be too long, lest it penetrate the wall of the vein after it is *in situ*. However, the needle should always be sharp. In the old days it was usual to employ a double-barreled container, one side for water and one side for the arsphenamine solution, this to make sure that no drug was injected until the needle was safely in a vein. However, if a small amount of distilled sterile water be first put into the container so that the tube is filled with it, it is totally unnecessary to employ a complicated double-barreled container. The container may either be hung upon a hook, or placed in a special stand that can be elevated so as to increase the pressure in case the flow be too slow.

The Tourniquet.—A tourniquet is almost invariably employed so as to engorge the vessels selected and make entrance to them easier. Far the best tourniquet I have found to be the armpiece of a blood pressure apparatus, for this will give any desired amount of pressure, will not hurt the arm, and can easily be released.

Selection of Vein.—Ordinarily the median basilic vein is selected for this is one of the largest and most easily entered. If this be not large, a vein in the neighborhood of the elbow should always be selected, for here the veins are firmly bound down. It must always be remembered that a large flabby vein, or one that rolls easily under the skin is much more difficult to inject than a smaller firm vein. At times when no vein can be seen it is possible to use a vein in the wrist or hand, but it should always be remembered that it is very difficult to inject more than 50 c.c. into such a vein; when one attempts to inject more fluid he will usually find that for some mysterious reason it will suddenly cease to flow. At times if the arm will be vigorously slapped the veins will become more prominent. In case of emergency I have used a vein in the ankle, and in children the

jugular vein is often employed. Under no circumstances should the vein be cut down upon unless absolutely necessary. In the first place the patient is branded for life, in the second place the vein is usually obliterated and can not be used again, and in the third place it is nearly always unnecessary. I have repeatedly seen a vein entered when only its position could be surmised.

Preparation of Patient.—The patient should always be instructed to eat but little during the day, and to have the bowels thoroughly moved. For the injection he may be sent to a hospital or the treatment given at home or in the office; with care the last is safe provided that he has not far to go and that he can take a carriage or automobile home. There are some physicians who feel that arsphenamine should only be given in the hospital, but in a well-equipped office I do not hesitate to give it. The patient is best given the injection while lying with the arm outstretched; he must always be put in a comfortable position, and care must be taken that there are no tight clothes that obstruct the venous return from the arm. The skin area surrounding the selected vein is swabbed with a 50 per cent solution of iodine which is allowed to remain for five minutes, and then removed with alcohol so that the vein can be better seen. After the injection the patient is instructed to eat but little and to lie down as much as possible for the remainder of the day.

Technic of Injection.—Three points in the injection are to be especially emphasized: the operation must be aseptic, no arsphenamine must be allowed to flow through the needle until it is within the vein, and upon withdrawal of the needle none must be allowed to escape into the wound. Once the apparatus is ready and the tourniquet is tightened the needle is inserted into the skin, and allowed to rest for a moment, then it is plunged directly into the vein, being held parallel with the course of the vein in so doing. Upon entering the vein pain at once ceases, the needle slides easily forward, and upon slight lateral movement the vein can be seen to move with the needle, and lastly blood will often flow back into the tubing. Then, and then only should the solution be allowed to flow; an injection should take about five minutes, and when the solution is almost out of the container a little sterile distilled water should be added, so

that this will be flowing through the needle when the latter is removed.

Minor Accidents Associated with Intravenous Injections.—At times the needle may not be within the lumen of the vein; there are three possibilities of error, the needle may never have entered the vein, the needle may pass entirely through the vein, or merely the sheath of the vein may be entered: in all of these cases the needle will not move forward freely. In the first two instances immediately the fluid begins to flow there will be a swelling near the tip of the needle and considerable pain to the patient. When the sheath of the vein is entered the solution will flow very slowly and there is pain, but no visible effusion. In any case the result is a very sore arm, provided that any of the drug has entered the tissues, whereas the water will cause but a trifling inconvenience. When any amount of arsphenamine has escaped a hard, firm, doughy swelling, of a livid red color will be manifest within twenty-four hours; this is intensely painful. This may gradually absorb within two weeks, or necrosis may result. I have seen an arm permanently disabled through such an accident. Rather harder to understand are the cases where the needle is perfectly in position, but when upon the next day a condition similar to the one just described arises. It is possible that the tip of the needle has nicked the wall of the vein from within, and it is just conceivable that some veins may be slightly porous to arsphenamine. Fortunately such accidents are very rare; I have encountered but three instances.

At times a needle will apparently enter a vein, usually a large soft one, easily, but immediately a hematoma will develop. In such instances the wall has, of course, been injured, and it is better to select a new vein. In two instances where there was but one vein available I have again entered the same vein, and there has been no subsequent trouble, but there is grave danger of the solution escaping through the rent. A hematoma will spontaneously resolve in a couple of days, and usually the vein is not permanently closed.

One of the most difficult of the situations arises when the solution ceases to flow during the injection. This may be due to too much venous obstruction on the upper arm, to the needle

entering the sheath of the vein from within, or to an obstruction within the tubing or needle; at times a clot may form at the tip of the needle. In some instances, especially in the case of very small veins, such as those of the wrist, there is no apparent reason for this failure, but nevertheless it is a not uncommon occurrence. When a patient has small veins I now make the habit of using the arsphenamine in more concentrated form, not over 40 c.c. inasmuch as it is usually possible to inject this amount before trouble develops. The first thing to do if the fluid begins to flow slowly is to make sure that there is no compression on the upper part of the arm, and the next to see whether the needle moves freely. In many instances it is necessary to use a new vein to continue the injection.

Occasionally without apparent reason the vein will become occluded after injection, due to thrombosis; too much alkali used in neutralizing may do this, but that this can not be the only cause is proved by the fact that it has occurred after the injection of neoarsphenamine as well as arsphenamine. At times this thrombosis may be tunneled so that it will not be apparent to the eye, for the blood still flows, but it can then be felt as a firm, hard cord. Care must be taken not to select such a vein for the injection, for to successfully enter it is a matter of both difficulty and pain.

The immediate reaction, associated with vasodilatation and tingling, has already been discussed. It is well to have a sterile hypodermic and a solution of 1:1000 adrenalin at hand for such an emergency. An injection of 5 to 10 minims will usually cause the symptoms to disappear at once.

Administration by Mouth.—Schamberg, Kolmer, and Raiziss[140] have recently shown that when arsphenamine is administered in enteric capsules it is absorbed by the blood; this has been proved experimentally upon animals, and has been tested out upon man. They recommend the following formula:

Arsenobenzol	0.03 gm.
Sodium thiosulphate	0.015 "
Bismuth subgallate	0.12 "

Sig: One after each meal with water.

The sodium hydrosulphite is added to prevent oxidation, and the bismuth to lessen the likelihood of inducing diarrhea.

Regarding the indication and limitations for the use of arsphenamine by mouth the authors state: "We wish emphatically to disclaim any intention of advocating the use of salvarsan by mouth as a substitute for intravenous or intramuscular administration. Where these avenues of introduction of the drug into the system can be employed they are far superior to oral ingestion. Syphilis should be treated with as massive doses of spirocheticides as can be given with complete safety to the patient. * * * In such cases salvarsan can be administered in capsule form for a period of from two to six weeks, after which its use should be interrupted for several weeks; its employment may be later resumed.

"Another indication for the use of salvarsan capsules is as a supplementary treatment to intravenous administration.* * * If after a period of three days following an intravenous injection the capsules are administered, a continuous source of the drug may be supplied to the blood." This form of treatment may also be of use to persons who are forced to pass from under the physician's care for a space of several weeks. Also, as Schamberg suggests salvarsan by mouth is in all probability more vigorous in its action than is mercury given by the same avenue, and possibly even than mercury administered by injection, since it is much less toxic to the system.

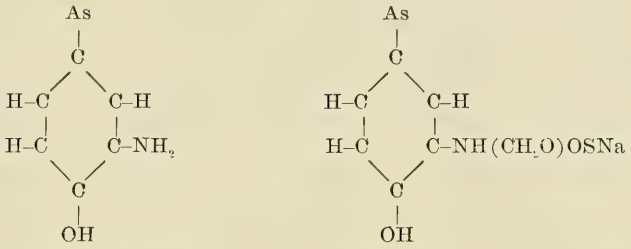
Administration by Suppositories.—Bagrow first employed salvarsan by this method, and lately we hear reports upon this method of administration, but as yet the value is unproved.

Dosage.—At first arsphenamine was employed in doses of about 0.3 grams, then there was a gradual reaction and 0.6 grams became the average dose: at the present time the pendulum has swung back and it is employed in average doses of about 0.006 grams per kilo of body weight, that is, a man weighing 160 pounds would receive 0.4 grams. In early cases where we are trying for a radical cure we usually employ 0.6 grams, after a rather smaller initial dose. In cases of long standing it is customary to start with a small dose, and this is best preceded by mercury, as there is then less danger of neurorecurrences.

Neosalvarsan, or "914," was marketed by Ehrlich a few months after the introduction of salvarsan, because consider-

able difficulty was found by some physicians in preparing the original Ehrlich preparation.

Composition.—Chemically neoarsphenamine is dioxydiamido-arsenobenzene-monomethane sulphinate of sodium. The structural formula is



A further report on the chemistry may be found in the report of the Council on Pharmacy and Chemistry of the American Medical Association,[141] and in McDonagh's[142] book. According to the manufacturers neoarsphenamine contains only two-thirds as much arsenic as does arsphenamine, and that according to other chemists is in a "masked" form. Neoarsphenamine is a neutral salt and does not require the addition of sodium hydroxide.

Action of Neoarsphenamine.—In general it may be stated that the action of neoarsphenamine is similar to that of arsphenamine. However, Schamberg,[143] in his experimental work upon animals has found that it is not nearly so effective as is the original preparation.

Contraindications for Neoarsphenamine.—In general it may be said that the contraindications for the use of neoarsphenamine are the same as for arsphenamine.

Untoward Effects of Neoarsphenamine.—It is generally believed that neoarsphenamine does not cause as many reactions as does arsphenamine. Ormsby[144] has confirmed this point by noting that 20 per cent of all patients reacted after arsphenamine and only 8 per cent after neoarsphenamine. There are practically no immediate reactions, but the symptoms of encephalitis may supervene, and quite a number of deaths have been reported. It should always be remembered that neoarsphenamine can not be allowed to escape into the tissues any

more than arsphenamine: the results are practically the same. Since using neoarsphenamine in concentrated form I have found a marked diminution in the number of reactions that result. Leredde[145] has given a review of the literature to date.

Clinical Results from Neoarsphenamine.—The majority of observers believe that the clinical results from neoarsphenamine are equally as good as those from the older preparation.

Serologic Results from Neoarsphenamine.—The majority of physicians feel that arsphenamine gives better serologic results than does neoarsphenamine. Whitehouse and Clarke[146] obtained 20 per cent more permanent negative Wassermanns with arsphenamine than with neoarsphenamine. Nelson and Haines[147] reported an even greater discrepancy. Ormsby[148] likewise considers the older preparation as the more efficient. Trimble and Rothwell[149] believe that neoarsphenamine is the better, but the weight of evidence is certainly against them.

Technic of Injection.—Neoarsphenamine is best given in from 10 to 20 c.c. of sterile distilled water, and the injection may be made with an ordinary Luer or Record syringe, to the tip of which is fitted a bit of rubber tubing, so as to give flexibility to the needle. In case the veins are very small Thompson[150] has suggested the use of two syringes, one filled with water and one with neoarsphenamine solution, and both connected to one needle by means of a two-way stopcock. The neoarsphenamine is dissolved in distilled water and then is at once ready for use.

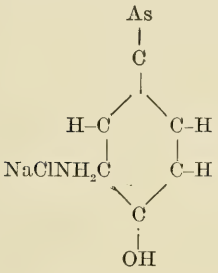
Dosage.—The dosage of neoarsphenamine is one-third larger than that of arsphenamine; a man weighing 160 pounds should receive 0.6 grams.

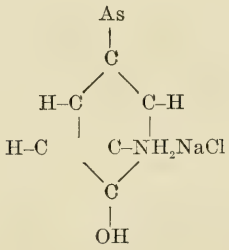
Route of Administration.—The intravenous route is to be preferred in all cases; from sad personal experience I have found that neoarsphenamine is no more fitted for intramuscular injection than is arsphenamine. Wechselmann[151] insists that the subcutaneous route is the best, but as usual his opinion must be taken *cum grano salis.*

Comparison of Arsphenamine and Neoarsphenamine.—Unquestionably neoarsphenamine is easier to administer and gives less discomfort to the patient than does arsphenamine, but also it is not so efficient a treponemicide and does not influence the

Wassermann so well. In private practice I exclusively employ the older preparation, but for dispensary work I prefer the neo.

Sodium Salvarsan.—Within the past three years a new preparation, sodium, or natrium, salvarsan has been extensively employed by some of our German confreres, but so far none has been available in America. This drug is said to combine the ease of preparation of neoarsphenamine with the therapeutic efficiency of the old arsphenamine. Thompson states that it is made by allowing sodium hydroxide to act upon arsphenamine, thus forming the disodium salt, which is then precipitated. The structural formula is:





For further information the reader is referred to the writings of Loeb,[152] Schumacher[153] and Wechselmann.[154]

Commercial Arsphenamines.—Since the outbreak of the war and the impossibility of securing sufficient salvarsan syphilologists have found that the drug could be equally well manufactured by others than the original German manufacturers.

Arsenobenzol.—Schamberg and his fellow-workers at the Dermatological Research Laboratories have succeeded in producing an arsphenamine that is clinically and serologically just as efficient as is the German preparation. The only point of disadvantage is the fact that it does not dissolve with avidity. The following technic, as recently recommended to me by Schamberg, may well be adopted. The tube is broken and the arsenobenzol dropped into about 25 c.c. of very hot water; this is then boiled until the substance goes into solution; the flask or beaker containing the solution is then placed in cold water until cool, and then is neutralized. Then it is filtered and injected just as in the original salvarsan. The majority of men who have

worked with arsenobenzol prefer it to salvarsan as being less toxic. The following writings may be consulted: Schamberg,[155] Ormsby,[156] Brayton,[157] and Wile.[158] My own experiences coincide with the above; I found a number of patients who reacted severely to salvarsan, but who did not react to arsenobenzol.

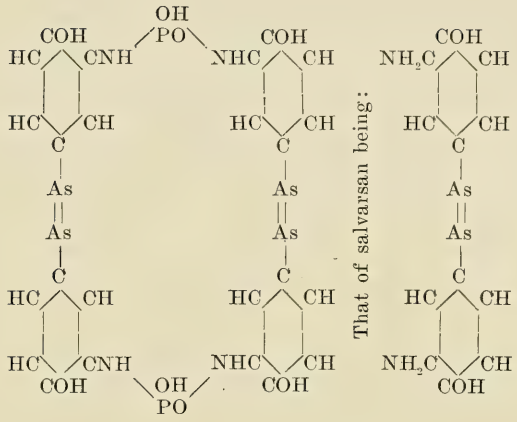
American-made Salvarsan.—This preparation is made and marketed by a New York firm. A number of excellent observers have had considerable trouble with the drug. Ormsby, a most reliable man, states: "Immediately after the New York company began the manufacture of salvarsan we received a number of ampules for experimental use. We gave a number of injections to a small number of patients, all of whom reacted severely during or immediately after the injection of the drug. The reactions were so severe that the few remaining ampules have never been used." (Ormsby and Mitchell: Skin and Venereal Diseases, Practical Medicine Series, 1918, p. 221.) Sargent has also had trouble with the preparation (Jour. Amer. Med. Assn., March 30, 1918). On the other hand, Baketel (Amer. Jour. Syph., July, 1918) and others have reported excellent results. Personally I have had no experience with the product.

Diarsenol.—Diarsenol is manufactured by the Synthetic Drug Company of Toronto, Ontario, and has about the same action as salvarsan. A number of observers have reported toxic effects from this preparation, Cook[159] in particular having had some unfortunate experiences. However, the preparation has proved eminently satisfactory in the hands of a number of men, including myself, although it is more toxic than arsenobenzol.

English and French arsphenamines are reviewed by Ffrench[160] in the London letter to the *Journal of the American Medical Association.* He found that both were reasonably satisfactory, and that the French preparation gave rather fewer reactions than any substance he had ever employed.

Galyl.—Galyl is a French substitute for salvarsan discovered by Mouneyrat. Chemically it is tetraoxydiphosphoaminodiarsenobenzene, with the structural formula as given on p. 629.

The percentage of arsenic is 35.3. It is dissolved in saline solution to which sodium carbonate is added in the proportion of about 20 grams per liter. Reports concerning it have been



published by Balzer,[161] Dudley,[162] Foerster,[163] Laveran and Roudsky,[164] and Spence.[165] In general it seems to act about as arsphenamine does but to be less toxic.

Choice of Preparations.—Personally I consider arsenobenzol as made by the Dermatological Research Laboratories to be the least toxic preparation, next I should rank neosalvarsan, next salvarsan as it was originally sent to this country, next diarsenol and last the salvarsan that has been shipped to America since the outbreak of the war; in the hands of other observers[166] the recent supply of German salvarsan has proved very toxic.

Treatment of Syphilis

In order to treat syphilis it is necessary to have an accurate conception of the pathology of the disease. It must be remembered that by the time the chancre appears the causal organism can also be found in many of the lymphatic structures of the body. This is the condition during the primary stage. Even before the secondaries develop it is probable that the organisms can be found in the blood and hence in all organs of the body, for it must take at least a few days after the treponemata are lodged in the tissues before the superficial lesions appear. During the eruptive period it is common to think of the lesions as being superficial, but this must be a mistake, for it is known that at this time the spinal fluid frequently shows alterations, and bone pains and various visceral manifestations are not uncommon.

The secondary stage proper is one, then, of widespread dissemination of the organisms and they are present in great numbers. During the late stages there are usually but few of the treponemata present, but owing to a lessened resistance upon the part of the tissues they are very apt to cause deeper and more serious lesions; also certain of the lesions may have a reduced blood supply, owing to obliteration of the arteries and they may also be more or less encapsulated in fibrous tissue.

Treatment of the Primary Stage.—Owing to the fact that the organisms have already spread beyond the initial lesion at the time it makes its appearance, it is useless to remove this locally, although such removal is advised by some eminent men on the grounds that it is one focus the less; to me this seems absurd when we remember that there are dozens of other foci already established. I feel that the local treatment of the chancre should consist exclusively of the local use of calomel, or other mercurial, either in the form of an ointment or a powder. During the chancre period, before the lesions are well established is the time to attempt a radical cure, and this is done by the means of repeated doses of arsphenamine, often combined with mercurial treatment, preferably by injection. Pollitzer[167] formerly recommended giving three intravenous injections of 0.6 grams of arsphenamine on three successive days, following with a course of twelve mercurial injections. Fordyce[168] recommends a course of five or six injections at intervals of from one to two weeks in average doses of 0.4 grams, together with 20 to 30 injections of a soluble mercurial salt at one- or two-day intervals, or twelve injections of an insoluble salt at weekly intervals. Two such courses are usually given. Many other men have recommended more or less similar treatment. Personally I believe that the first course is the all important one, and that if this fails a second course is most unlikely to succeed. I usually adopt the following scheme, provided the patient can take arsphenamine well. Just as soon as the diagnosis is made, and there is no excuse for not making this just as soon as the patient appears, a dose of 0.4 grams of arsphenamine is given. Then seven more injections of 0.4 grams arsphenamine are given, the first four at three- to five day intervals, and the last four at weekly intervals; this should be accompanied by a course of mercurials; the

first mercurial injection should unquestionably be a soluble salt so that immediate action can be got; either the same or the next day an insoluble salt should be given, and then either the soluble or the insoluble salts may be administered until twelve injections have been given. There is absolutely no advantage in giving the iodides at this time. Of course the weight, urine, and general well being of the patient must be most carefully watched and the number and size of the doses of both arsphenamine and the mercurials governed accordingly, according to the rules already laid down. Then four more arsphenamine injections are given, and then another course of mercury.

Results of Treatment of the Primary Stage.—There is much discussion but very few reliable statistics as to the number of permanent cures that are secured as the result of this intensive form of treatment. Personally, I feel that the ordinary criteria for cure, that is, a negative provocative Wassermann at the end of one or two years, is an indication, but by no means an absolute proof that the disease is eradicated, for I[169] have seen relapses within two months of the time that a two year provocative Wassermann was done. However, the growing list of reinfections following such intensive treatment is the best indication that some of the cases must be cured; at any rate we know beyond peradventure that a patient who has received such treatment usually shows neither clinical nor laboratory signs of syphilis for some years to come. I do feel very strongly, and I am sure that every syphilologist agrees with me, that a patient so treated has at least a good sporting chance of having the disease completely cured.

Treatment During the Secondary Period.—I feel that practically the same treatment should be given during the secondary eruptive period as during the primary stage, although, of course, the chances for a radical cure diminish in proportion to the duration of the disease. If the patients are treated during the first week or two of the eruptive period the chances for permanent cure are fair, probably about 33 per cent, although this is a rough guess. If treatment is started later than four weeks after the appearance of the florid stage the chances for a permanent cure are probably slight. It is certain that such cases should receive two courses, at intervals of about two to four months.

Treatment During the Late Stages.—Personally I feel convinced that no patient who has progressed to the period of developing late syphilis can be radically cured: however, the possibility of such an event must be borne in mind, and the patient given his choice of two or three courses, such as have already been described. However, I usually advise that he take only sufficient treatment to keep his Wassermann negative and to keep him from showing any symptoms of syphilis. Such a patient should have a Wassermann test at least every six months. It is difficult to explain the remarkable results that sometimes follow the administration of a small amount of treatment. I recall one woman who had late active lues, with a strongly positive Wassermann. She was given but one injection of neoarsphenamine and two months of mercury by mouth, and for three years has shown no evidence of the disease; clinically and serologically she is cured, but the possibility remains that in some of her organs the trouble is still active. It is best to first administer mercury, and later the arsphenamine; this lessens the danger of neurorecurrences.

Value of Thorough Treatment.—It may be objected that there is but little use in treating syphilis if we can not cure the disease. This is not so; clinical experience has taught us that the cases that are efficiently treated are by no means so prone to develop late lesions as are the cases that have undergone insufficient treatment. Wile and Elliott[170] have shown that out of 120 cases of late syphilis but one had received what we now believe to be proper treatment. Years ago Fournier emphasized the same point.

Value of the Wassermann in Controlling Treatment.—While the Wassermann is by no means an infallible guide, it remains the best index that we have as to the progress of the disease in cases where no clinical signs are manifest. Every syphilitic patient who has recently undergone treatment should have his blood examined at least once every three months for the first year, and once each six months for, probably, ten years thereafter. If the laboratory signs and the clinical signs remain absent, we are probably safe in administering no further treatment, but a positive Wassermann is always an absolute indication for more treatment.

Wassermann-fast Cases.—By Wassermann-fast cases are meant those cases which persistently run a positive complement-fixation reaction, in spite of thorough treatment. In all such cases it is more than probable that there is some focus of infection, and we are just beginning to learn that this is frequently in the nervous system, and that intraspinous medication will often render the blood negative. However, the focus may be in some other organ. Pollitzer[171] has emphasized the fact that if treatment be long enough continued the vast majority of such cases can be rendered Wassermann negative. In many such cases shortening the period between the administrations of arsphenamine is extremely effective. This I have verified from personal experience.

Value of the Luetin Reaction in Controlling Treatment.—We are just beginning to learn that the luetin test has more limitations than we previously thought, for it has been shown that potassium iodide will frequently sensitize a patient so that he will give a positive reaction even though he has not syphilis. Hence the luetin should never be used in persons who have recently taken any of the iodides. If these can be eliminated it is probable that a positive luetin must be viewed in the same light as a positive Wassermann and treatment continued until it becomes negative.

Reasons for the Failure of Treatment to Cure.—Arsphenamine will experimentally kill *in vivo* all of the syphilitic organisms with which it comes in contact, but clinically it will not always cure syphilis. Mercury will not kill the organisms without also damaging the host. Why will not arsphenamine always cure the disease? As already indicated McDonagh believes that the causal organism has a complicated life cycle, and that arsphenamine will only kill one or two phases. A second explanation is that the organisms become encapsulated so that the medicine can not reach them, and the third explanation is that the organisms become drug-fast. This last has recently been proved untrue.

Criteria of Cure.—One of the most difficult things to know about syphilis is to know when the patient is cured, that is, permanently cured. Certain it is that when he is Wassermann negative he is not necessarily well forever. The generally accepted criteria are that there must be no physical signs or symp-

toms of the disease, that he must have been Wassermann negative for at least two years, that the luetin be negative and that the spinal fluid show no abnormalities. However, Warthin's often-quoted work has shown that autopsies upon some of the best treated and supposedly cured cases have revealed the presence of the treponema and of active, although small, syphilitic lesions. Personally, I sometimes feel as though the only real criterion of cure is the presence of a reinfection, and even here the causal organisms must be demonstrated in abundance or a local recurrence, chancre redux, would have to be thought of. Only the future can tell us just exactly what are the proper criteria.

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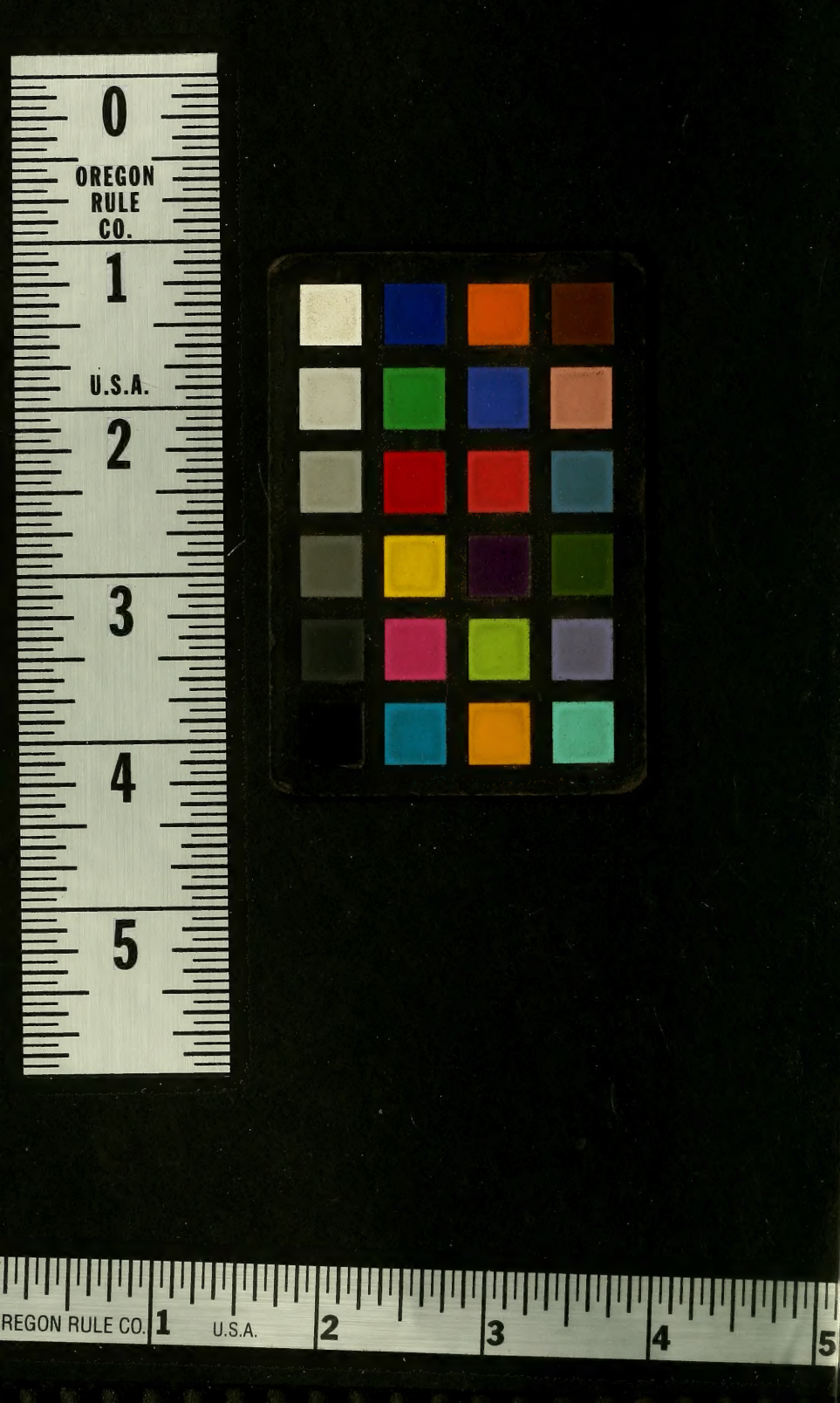
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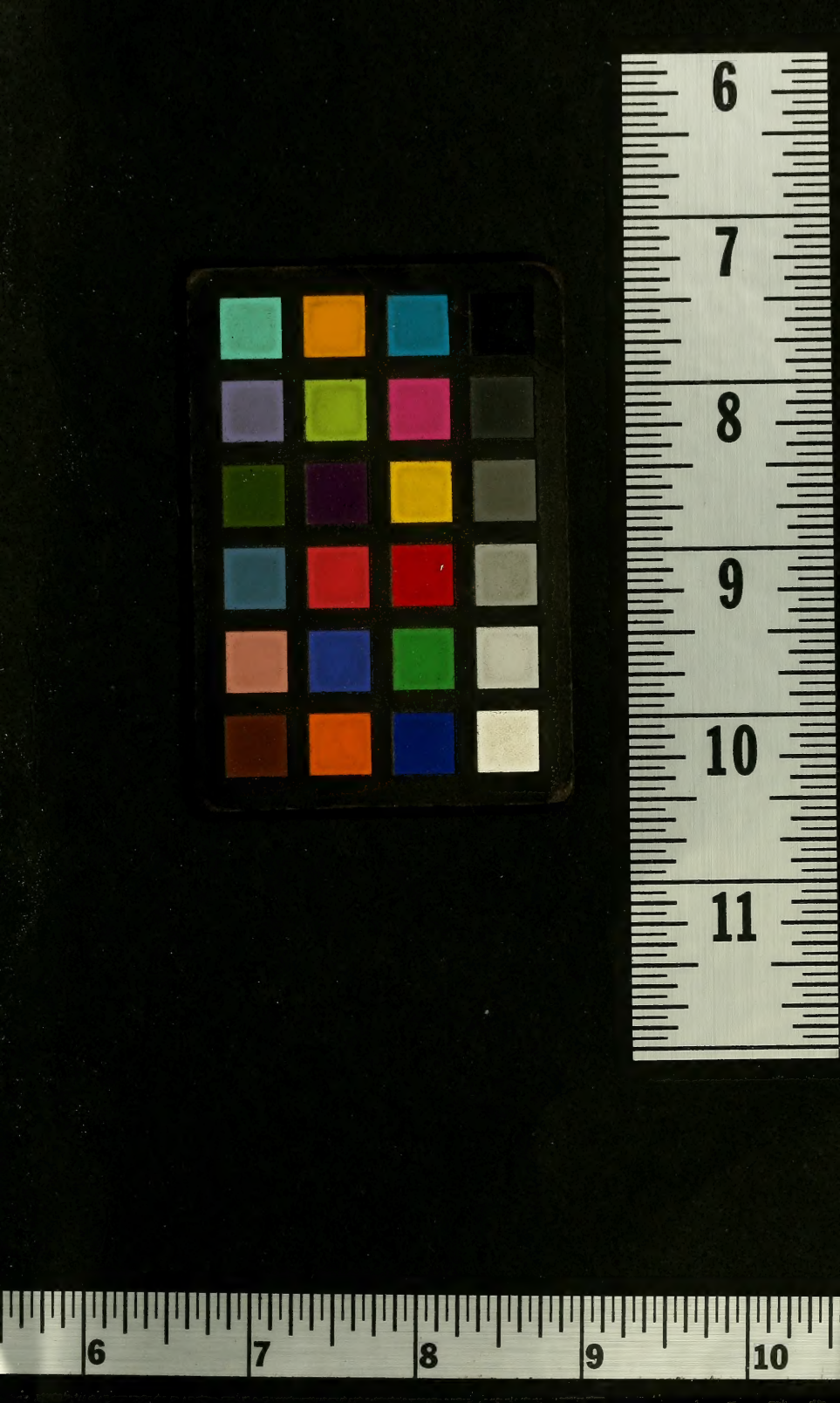
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